HTA Austria
Austrian Institute for
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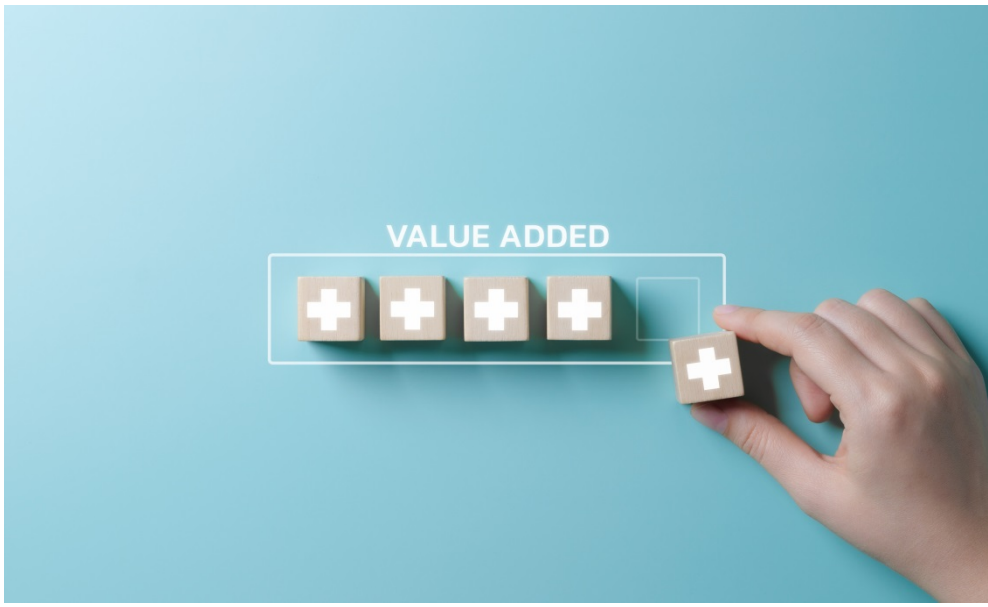
Threshold Values in Health Economic Evaluations and Decision-Making



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Threshold Values in Health Economic Evaluations and Decision-Making

Vienna, December 2024

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List of abbreviations

ABPI.....Association of the British Pharmaceutical Industry
AMCP .....Academy of Managed Care Pharmacy
AOTMiT .....Agency for Health Technology Assessment and Tariff System
AS .....Absolute Shortfall
ASVG.....General Social Insurance Act/ Allgemeines Sozialversicherungsgesetz
ATMPs.....Advanced Therapy Medicinal Products
AUD .....Australian Dollar
AUS .....Australia
BGN .....Bulgarian Lew
BIT .....Budget Impact Test
BRA.....Brazil
BRL.....Brazilian Real
B-VG.....Federal Constitutional Act/ Bundesverfassungsgesetz
CAD .....Canadian Dollar
CADTH .....Canadian Agency for Drugs and Technologies in Health
CAN .....Canada
CBA.....Cost-Benefit Analysis
CCA.....Cost-Consequence Analysis
CDA-AMC....Canada's Drug Agency
CEA.....Cost-Effectiveness Analysis
CET.....Cost-Effectiveness Threshold
CFES.....Czech Pharmacoeconomic Society
CHF .....Swiss Franc
CHN.....China
CMA.....Cost-Minimisation Analysis
CUA .....Cost-Utility Analysis
CVD .....Cardiovascular Diseases
CZE.....Czech Republic
CZK.....Czech Koruna
DA .....Decision Analysis
DALY.....Disability-Adjusted Life Year
DHSC.....Department of Health and Social Care
DKK.....Danish Krona
EAW/E&W...England and Wales
EFA .....Efficiency Frontier Approach
EKO.....Code of Reimbursement/ Erstattungskodex
EQ-5D .....EuroQoL
ESP.....Spain
EST .....Estonia
EU .....European Union
EUR .....Euro
evLYG .....Equal Value of Life Years Gained
GBP.....British Pound
GCEA.....Generalised Cost-Effectiveness Analyses
GDP .....Gross Domestic Product
GRC .....Greece
HEE .....Health Economic Evaluation
HEK.....Drug Evaluation Committee/ Heilmittelevaluierungskommission
HICs.....High-Income Countries
HIC .....High-Income Countries
HID.....Highly Innovative Drugs
HIQA .....Health Information and Quality Authority
HITAP .....Health Intervention and Technology Assessment Program
HLE .....Health Life Expectancy
HLY .....Healthy Life Years
HRQoL .....Health-Related Quality of Life
HTA .....Health Technology Assessment
HUF .....Hungarian Forint
HUN.....Hungary
ICD .....International Statistical Classification of Diseases and Related Health Problems
ICER .....Incremental Cost-Effectiveness
IKEV .....Inkrementelles Kosten-Effektivitäts-Verhältnis
IKNV.....Inkrementelles Kosten-Nutzwert-Verhältnis
ILS.....Israel Schekel
IRL.....Ireland
ISPOR.....Professional Society for Health Economics and Outcomes Research
JPN.....Japan
JPY .....Japanese Yen
KAKuG .....Federal Hospitals Act/Kranken-anstalten und Kuranstaltengesetz
KOR .....South Korea
KRW .....South Korean Won
LL.....Leitlinie

LMICs.....Low-Income Countries
LVT.....Latvia
LY.....Life Years
LYG.....Life-Year Gained
MAH.....Marketing Authorization Holder
NB.....Net Benefit
NHIM.....National Health Insurance Model
NHS.....National Health Service
NICE.....National Institute for Health and Care Excellence
NIHR.....Norwegian Institute for Public Health/National Institute for Health Research
NLD.....Netherlands
NLT.....Nya läkemedelsterapier/ New Drug Therapies
NOK.....Norwegian Krona
NOR.....Norway
NZD.....New Zealand Dollar
Pat.....Patients/Patient*innen
PB.....Programme Budgeting
PBAC.....Pharmaceutical Benefits Advisory Committee
PBCs.....Programme Budgeting Categories
PEG.....Pharmacoeconomic Guideline
PER.....Pharmacoeconomic Recommendation
PFS.....Progression-Free Survival
PICo.....Problem, Interest, and Context
PLN.....Polish Zloty
POL.....Poland
PPP.....Purchasing Power Parity
Pref./Präf.....Preferences/Präferenzen
PRT.....Portugal
PS.....Proportional Shortfall
PTC.....Pharmaceutical and therapeutic committees/Arzneimittelkommission
PVT.....Pharmacoeconomic Value Threshold
QALY.....Quality-Adjusted Life Year
QLM.....Qualitative Modifier
QNM.....Quantitative Modifier
RMB.....Renminbi
RQ.....Research Questions
RVO.....Reich Insurance Code/Reichsversicherungsordnung
SAVE.....Saved Young Life Equivalent
SBU.....Statens beredning för medicinsk och social utvärdering/Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCT.....Scotland
SD.....Standard Deviation
SEK.....Swedish Krona
SF-12D.....Short-Form 12-Dimension
SF-36D.....Short-Form 36-Dimension
SF-6D.....Short-Form Six-Dimension,
SG.....Standard Gamble (SG)
SGD.....Singapore Dollar
SMC.....Scottish Medicines Consortium
SOC.....Standard of Care
SubG.....Submission Guideline
SÚKL.....Státní ústav pro kontrolu léčiv/ State Institute for Drug Control
SVK.....Slovak Republic
SVN.....Slovenia
SWE.....Sweden
TCL.....Therapeutic Criteria Levels
TCL.....Therapeutic Criteria Levels
THA.....Thailand
THB.....Thai Baht
TLV.....Tandvårds- och läkemedelsförmånsverket/Dental and Pharmaceutical Benefits Agency
TR.....Temporary Reimbursement
TTO.....Time Trade-Off
TWD.....Taiwanese Dollar
USA.....United States of America
USA.....United States of America
USD.....United States Dollar
US-ICER.....Institute for Clinical and Economic Review
VAS.....Visual Analogue Scale
VO-EKO.....Rules of Procedures Code of Reimbursement/Verfahrensordnung Erstattungskodex
WHO.....World Health Organisation
WOSCOPS...West of Scotland Coronary Prevention Study
WTP.....Willingness to Pay
ZIN.....Zorginstituut Nederland/Dutch National Health Care Institute
ZZZS.....Zavod za zdravstveno zavarovanje Slovenije/Health Insurance Institute of Slovenia

Executive Summary

Background

decision-making & resource allocation in healthcare using health economic evaluations (HEE) & threshold(s)

In healthcare systems worldwide, decision-makers face the complex challenge of optimally allocating resources. Various aspects, particularly efficient resource utilisation, play a central role in prioritising healthcare services and reimbursement decisions. The incremental cost-effectiveness ratio (ICER) threshold serves as a crucial reference point for decision-makers to assess whether an intervention demonstrates an appropriate relationship between costs and benefits, forming an important basis for a sustainable healthcare system.

Methods

literature review & assessment of threshold applications across healthcare systems

The study analysed literature (empirical and theoretical), policy documents, health economic guidelines from various countries, and expert knowledge. The research aimed to explain theoretical foundations and implications of thresholds in health economic evaluations, provide an overview of countries utilising such thresholds, identify complementary factors – so-called modifiers, and analyse their transferability to the Austrian healthcare context.

Results

Theoretical Foundations and Practical Implications

thresholds reflect opportunity costs within budget constraints

The ICER threshold represents a fundamental economic concept of opportunity costs, interpreted both as foregone benefits from alternative resource use and as additional resources society is willing to invest in health effects. A key distinction exists between fixed and flexible budgets in this context. With fixed budgets, the threshold theoretically emerges from maximising health benefits within predetermined budget constraints. However, this approach is rarely implemented as a pure "league table" approach in practice due to high information requirements. Instead, specific estimation methods are employed to approximate "true" opportunity costs.

simplified threshold application reflects practical needs despite theoretical limitations

In decision-making contexts, the threshold is typically treated as a fixed value, regardless of budget type. Whilst this simplification facilitates practical application, it overlooks important theoretical distinctions. True opportunity costs can never be fully captured, as the underlying theoretical assumptions are never completely fulfilled in reality. This pragmatic approach to threshold implementation reflects the practical constraints and complexities of healthcare decision-making whilst acknowledging the limitations of thresholds.

Methods for Determining Thresholds

diverse approaches to threshold determination & implementation

Several methodological approaches exist, including empirical methods for fixed and flexible budgets, GDP-based approaches (particularly WHO-CHOICE), willingness-to-pay methods, and the efficiency frontier approach. Each method has specific advantages and limitations, with varying data requirements and implementation challenges.

Country Overview and Descriptive Analysis

international threshold practices: 24 countries employ diverse threshold systems (e.g., explicit vs. implicit etc.)

Amongst 39 analysed countries, 24 (62%) employ thresholds in their decision-making processes, with two-thirds being European countries. Seven countries, including Estonia, England and Wales, Ireland, Poland, Slovakia, Slovenia, and Thailand, utilise explicit thresholds, whilst 17 countries operate with implicit thresholds. Notably, eleven of the 24 countries employ either threshold ranges or multiple baseline thresholds, such as Canada's different thresholds for oncological and non-oncological interventions.

thresholds & calculation methods vary significantly across countries

values from € 4,000 to € 142,450 per QALY

The methods for determining thresholds show considerable variation: twelve countries are not transparent on their calculation methods, with nine employing GDP-based approaches and three countries – Australia, Latvia, and Spain – utilising empirical methods. The actual threshold values demonstrate significant variation, ranging from € 4,000 to € 50,000 per QALY, with an average baseline threshold of approximately € 28,500. Slovakia shows the highest threshold at € 53,900, whilst Thailand maintains the lowest at € 4,340. For countries employing threshold ranges, the average upper threshold reaches € 54,200, with the United States demonstrating the highest value at € 142,450.

inverse U-shaped relationship between thresholds & healthy life expectancy (HLE)

The descriptive analysis revealed interesting patterns between healthy life expectancy (HLE), GDP per capita, and thresholds across healthcare systems. A weak, inverse U-shaped relationship emerges between HLE and thresholds, with the positive association peaking at 70 years at a threshold of € 31,650 before declining. This relationship may suggest that there is an optimal level of threshold (around € 31,650) that maximises HLE, and that HLE declines as thresholds either increase or decrease from this optimal level.

calculation methods influence threshold-HLE relationship patterns

When analysed by calculation method, GDP-based thresholds maintain this inverse U-shaped structure, albeit weaker. For countries without specific calculation methods, the relationship suggests that the higher the threshold, the higher the HLE in the country, but at a decreasing rate.

GDP, system characteristics & country preferences may shape threshold variations

The relationship between thresholds and GDP per capita varies by method. GDP-based thresholds show a direct correlation, particularly influenced by the 'GDP factor', as evidenced by Slovakia and Poland's substantially higher thresholds due to their triple GDP factor. For countries without specific calculation methods, the relationship is less pronounced, with increasing threshold variance at higher GDP levels, suggesting that country-specific preferences and socioeconomic factors play a more significant role in high-income countries.

Modifiers and Additional Decision Criteria

threshold-modifying (quantitative) & decision-modifying (qualitative) modifiers complement thresholds

Of the 24 countries studied, 15 (62.5%) employ modifiers that either quantitatively alter the ICER or ICER threshold or qualitatively affect the reimbursement decision. These modifiers acknowledge that health maximisation and efficiency are not the only objectives of decision-makers and may not fully reflect societal preferences in resource allocation. Quantitative modifiers directly influence the health economic evaluation by affecting the ICER or threshold, whilst qualitative modifiers inform the deliberative decision-making process.

identification & analysis of 10 modification criteria: disease severity, rarity, equity, therapeutic alternatives etc.

Ten distinct modification criteria were identified, with disease severity and rare diseases being the most frequently applied, followed by equity considerations and availability of therapeutic alternatives. Twelve countries utilise quantitative modifiers that increase the threshold or ICER, whilst six countries have officially established qualitative modifiers. Three countries – Can-

ada, the Czech Republic, and England/Wales – employ both types of modifiers, demonstrating the potential for combined approaches in decision-making processes.

Discussion and Implications for Austria

HEE in Austria: from minor role to potential expansion

implementation challenges & decision needs for Austria

In Austria, health economic evaluations have so far played a minor role and have only formally been required in specific cases, primarily in the assessment of outpatient pharmaceuticals. With the recently passed law on assessing hospital drugs and those at the interface between the inpatient and outpatient sectors, they may play a more prominent role in future. Yet, neither setting has discussed the concept of cost-effectiveness thresholds. Whilst efficiency concepts *("Wirtschaftlichkeit")* are anchored in various laws, they are rarely operationalised concretely. For the more widespread and standardised implementation of economic evaluations (in combination with thresholds) in Austria, fundamental decisions are required regarding the future role of health economic evaluations, methodological design, threshold determination, and integration of additional decision criteria.

HEE implementation requires methodological foundation & public understanding

communication needed to differentiate rationing from rationalisation

A systematic implementation requires several key measures, including developing detailed methodological guidelines, the creation of adequate cost and benefit assessment methods, building capacity, and harmonising legal and scientific terminology. Implementing systematic health economic evaluations, including threshold operationalisation, will likely spark controversy as such measures are often perceived as rationing measures. Therefore, a proactive awareness strategy is recommended to clarify the distinction between cost containment (rationing) and efficient resource utilisation (rationalisation), whilst highlighting the advantages of transparent decision processes.

Limitations and Research Needs

limitations & need for further research on threshold relationships

The study acknowledges methodological limitations in country selection and modifier categorisation. The descriptive analysis provides initial insights but cannot fully explain complex relationships between variables. Furthermore, these results should not be interpreted as causal relationships but rather as simple correlations. Further research incorporating more complex models and additional country-specific factors is required.

Conclusions

efficiency considerations & ethical resource use in health care

Considering efficiency criteria in reimbursement decisions represents an ethical necessity in managing public resources. The central challenge lies not in whether but in how efficiency considerations and possible modifiers can be consistently and transparently integrated into reimbursement processes.

threshold implementation requires country-specific adaptation & preparation

International experience shows there is no universal "gold standard" for implementing thresholds. Each methodological approach has specific advantages and disadvantages and must be adapted to the national context. For successful implementation in Austria, various accompanying measures are required, including further research on methodological aspects, stakeholder sensitisation, and capacity building.

political decisions needed for threshold design despite implementation complexity

The evidence suggests that whilst implementing thresholds is complex, it can contribute to greater transparency and efficiency in the healthcare system. The final decision on specific design must be made at the political level, carefully weighing various methodological options and their implications.

Zusammenfassung

Hintergrund

gesundheitsökonomischen Evaluationen (HEE) Schwellenwerte als Instrumente für effiziente Ressourcenallokation im Gesundheitswesen

Im Gesundheitswesen stehen Entscheidungsträger vor der Aufgabe, Ressourcen bestmöglich einzusetzen. Dabei können mehrere Aspekte, unter anderem ein effizienter Ressourceneinsatz, eine zentrale Rolle bei der Priorisierung von Gesundheitsleistungen und Erstattungsentscheidungen spielen. Um Effizienz messbar und vergleichbar zu machen, haben sich verschiedene Methoden der gesundheitsökonomischen Evaluation etabliert. Ein bedeutsames Instrument in diesem Kontext ist der ICER-Schwellenwert (Inkrementeller Kosten-Effektivitäts-Verhältnis-Schwellenwert; kurz Schwellenwert). Dieser Schwellenwert dient als Orientierungsgröße, anhand derer Entscheidungsträger beurteilen können, ob eine Intervention ein angemessenes Verhältnis von Kosten und Nutzen aufweist. Er bildet damit eine wichtige Entscheidungsgrundlage für die nachhaltige Gestaltung des Gesundheitssystems.

Schwellenwert als Ausdruck von Opportunitätskosten

Der Schwellenwert repräsentiert dabei ein fundamentales ökonomische Konzept: Opportunitätskosten

doppelte Interpretation:

Opportunitätskosten im Kontext von Schwellenwerten können auf zwei Arten interpretiert werden:

- **entgangener Nutzen der nächstbesten Alternative** Zum einen spiegelt ein Schwellenwert den entgangenen Nutzen wider, der durch die alternative Verwendung dieser Ressourcen hätte entstehen können.
- **Maß gesellschaftlicher Investitionsbereitschaft in Gesundheit** Zum anderen die zusätzlichen Ressourcen, die eine Gesellschaft bereit ist, für einen zusätzlichen Gesundheitseffekt (beispielsweise in Form eines qualitätskorrigierten Lebensjahrs) aufzuwenden.

Opportunitätskosten umfassen auch nicht-finanzielle Ressourcen

Opportunitätskosten umfassen dabei nicht nur die direkten finanziellen Aufwendungen, sondern auch alle anderen relevanten Ressourcen, die durch eine Intervention (möglicherweise) gebunden werden.

Grenzen & Ergänzungsbedarf von Schwellenwerten in der Praxis

Allerdings hat die Anwendung von Schwellenwerten als alleiniges entscheidungsrelevantes Kriterium auch Einschränkungen: Es gibt keinen universellen bzw. „One-size fits all"-Schwellenwert, und die Herleitung basiert teils auf stark vereinfachenden Annahmen. Zudem berücksichtigen rein ökonomische Überlegungen nicht alle entscheidungs- und gesellschaftsrelevanten Faktoren wie Gerechtigkeit oder gleichen Zugang zur Gesundheitsversorgung. Daher nutzen verschiedene Länder unterschiedliche Ansätze – einige verzichten ganz auf gesundheitsökonomische Evaluationen, andere ergänzen sie um weitere Kriterien.

Methoden

Problemstellung

Analyse von Schwellenwerten: Bedeutung & mögliche Implementierung in Österreich

In Österreich spielen gesundheitsökonomische Evaluationen bei Erstattungsentscheidungen bisher eine untergeordnete Rolle. Auch wurde noch kein Schwellenwert definiert oder diskutiert. Angesichts der Herausforderungen für ein nachhaltiges Gesundheitssystem und der Einführung solcher Schwellenwerte in vielen europäischen Ländern ist es wichtig, das Konzept der Schwellenwerte im österreichischen Kontext zu verstehen und deren Vor- und Nachteile zu analysieren.

Projektziele

Der Bericht verfolgt folgende Ziele:

Fokus & Ziele des Berichts

- Erklärung der theoretischen Grundlagen, des Zwecks und der Auswirkungen von Schwellenwerten in gesundheitsökonomischen Evaluationen

theoretische Grundlagen

- Überblick über Länder, die gesundheitsökonomische Evaluationen mit Schwellenwerten für Erstattungsentscheidungen nutzen

internationale Praxis zu Schwellenwerten & Modifikatoren

- Identifikation von alternativen oder ergänzenden Faktoren (Modifikatoren) zu Schwellenwerten
- Analyse der Übertragbarkeit der Resultate auf das österreichische Gesundheitssystem und Ermittlung notwendiger Schritte für eine mögliche Implementierung

österreichischer Kontext

Forschungsfragen

Folgende Forschungsfragen sollen im Zuge des Berichts beantwortet werden:

Forschungsfragen:

4 zentrale Forschungsfragen: von Theorie zur österreichischen Praxis

FF1 Welche theoretischen Grundlagen und Auswirkungen haben Schwellenwerte für Entscheidungsprozesse?

FF2 Welche Methoden zur Schwellenwert-Definition gibt es und was sind deren Vor- und Nachteile?

FF3 Welche Länder verwenden Schwellenwerte und welche anderen Faktoren spielen eine wichtige Rolle?

FF4 Welche Rolle spielen Effizienzüberlegungen im österreichischen Gesundheitssystem und welche Schritte wären für eine Implementierung von Schwellenwerten notwendig?

Nicht Teil des Projekts ist eine rechtliche Analyse des österreichischen Rechtsrahmens bezüglich gesundheitsökonomischer Evaluation und der Anwendung von Schwellenwerten im Sinne einer Rechtsfolgenabschätzung.

keine Rechtsfolgenabschätzung

Methodische Vorgehensweise

Der Bericht basiert auf einer Auswertung der wissenschaftlichen Literatur (empirisch und theoretisch), politischer und entscheidungsrelevanter Dokumente, gesundheitsökonomischer Leitlinien aus verschiedenen Ländern sowie Expert*innenenwissen. Darüber hinaus wurde eine empirische Analyse der identifizierten Schwellenwerte und Modifikatoren durchgeführt. Die Bearbeitung des Berichts erfolgte schrittweise:

Literaturanalyse & Analyse der internationalen Anwendung von Schwellenwerten

- Übersicht über die Literatur und theoretische Grundlagen gesundheitsökonomischer Konzepte einschließlich gesundheitsökonomischer Evaluationen (Kapitel 3).

Literaturübersicht & theoretische Grundlagen der Gesundheitsökonomie;

- Identifizierung und Überblick über Länder mit Schwellenwerten und Modifikatoren sowie Beschreibung ihrer gesundheitsökonomischen Methoden im Erstattungsprozess (Kapitel 4).

Analyse Schwellenwerte & Modifikatoren;

- Empirische Analyse der Schwellenwerte und Modifikatoren (Kapitel 4).

empirische Analyse der Schwellenwerte;

- Überprüfung und Einordnung der Ergebnisse für das österreichische Gesundheitssystem (Kapitel 5).

Übertragbarkeit auf österreichisches System;

- Zusammenfassung und kritische Reflexion der Ergebnisse (Kapitel 0).

Qualitätssicherung des Berichts

Im Rahmen der Qualitätssicherung wurde der Bericht sowohl intern als auch von zwei externen Gutachter*innen überprüft.

kritische Reflexion & Schlussfolgerungen

Ergebnisse

Theoretische Grundlagen und praktische Implikationen

Schwellenwertermittlung: unterschiedliche Ansätze je nach Budgettyp

Ein wesentlicher Aspekt bei Schwellenwerten ist die Unterscheidung zwischen fixen und flexiblen Gesundheitsbudgets. Im Falle eines fixen Budgets ergibt sich der Schwellenwert theoretisch aus der Maximierung des Gesundheitsnutzens innerhalb des vorgegebenen Budgetrahmens. In der Praxis wird dies aber nicht „nach Lehrbuch" im Sinne eines „League Table"-Ansatzes durchgeführt, da dies mit einem hohen Aufwand und Informationsbedarf einhergeht. Aus diesem Grund kommen hier spezifische Schätzmethoden zum Einsatz, um die „wahren" Opportunitätskosten zu approximieren. Bei einem flexiblen Budget hingegen kann der Schwellenwert exogen festgelegt werden, was mehr Spielraum für Anpassungen bietet.

fixer Schwellenwert als pragmatischer Kompromiss, aber mit Limitationen verbunden

Im Entscheidungskontext wird der Schwellenwert zumeist als fester Wert behandelt, unabhängig von der Art des Budgets. Diese Vereinfachung erleichtert zwar die praktische Anwendung, vernachlässigt aber wichtige theoretische Unterschiede. Die wahren Opportunitätskosten lassen sich dabei nie vollständig abbilden, da die zugrundeliegenden, theoretischen Annahmen in der Realität nie vollständig erfüllt sind.

Methoden zur Bestimmung von Schwellenwerten

verschiedene Ansätze zur Schwellenwertermittlung

Für die Bestimmung von Schwellenwerten existieren verschiedene methodische Ansätze.

- Die *empirischen Methoden* unterscheiden dabei zwischen fixen und flexiblen Budgets:

  empirische Ansätze bei …

  - **… einem fixen Budget → marginale Produktivität der Gesundheitsausgaben**

    Bei fixen Budgets wird versucht, den Schwellenwert auf Basis der marginalen Produktivität (Grenzproduktivität) der Gesundheitsausgaben zu berechnen. Diesen Ansatz setzten etwa britische Forschende um. Er stellt hohe Ansprüche an Daten und Informationsbedarf.

  - **… einem flexiblen Budget → Berechnung mit makroökonomischen Daten**

    Für flexible Budgets existieren empirische Ansätze, die auf Gesundheitsausgaben und Lebenserwartungsdaten basieren. Hier werden zumeist makroökonomische Daten zur Berechnung länderspezifischer Schwellenwerte herangezogen. Allerdings weist dieser Ansatz methodische Schwächen auf, etwa hinsichtlich der Kausalität.

- **BIP-basierte bzw. WHO-CHOICE-Methode**

  Der *BIP-basierte Ansatz*, insbesondere die WHO-CHOICE-Methode, ist international am weitesten verbreitet – vor allem in Ländern mit niedrigen und mittleren Einkommen. Dieser Ansatz nutzt das Bruttoinlandsprodukt (BIP) pro Kopf sowohl als Proxy für entgangene Einnahmen durch Krankheit als auch als Indikator für die Ressourcenverfügbarkeit. Kritiker*innen bemängeln aber, dass diese Methode zu einem „zu hohen" Schwellenwert führt. Trotzdem findet er aufgrund seiner einfachen Berechenbarkeit weiterhin breite Anwendung.

- **gesellschaftliche Zahlungsbereitschaft bzw. Willingness-to-Pay (WTP)**

  Ein weiterer Ansatz basiert auf der *gesellschaftlichen Zahlungsbereitschaft* (Willingness-to-Pay). Dieser Ansatz berücksichtigt explizit die Präferenzen der Bevölkerung (Patient*innen oder Zahler*innen) und kann auch nicht-gesundheitsrelevante Aspekte miteinbeziehen. Die methodisch anspruchsvolle Erhebung dieser Präferenzen stellt jedoch eine Herausforderung dar.

- **Effizienzgrenzen-Ansatz: kein Schwellenwert aber Preisobergrenze**

  Der *Effizienzgrenzen-Ansatz* nutzt die aktuell effiziente Kombination verfügbarer Interventionen als Grundlage und ermöglicht die Berechnung von Preisobergrenzen. Dabei werden die eingesetzten Ressour-

cen bzw. das Budget nur durch die potenziellen Gesundheitsverbesserungen begrenzt, was diesen Ansatz besonders flexibel macht. Bis 2024 wurde dieser Ansatz in Deutschland angewendet.

Länderübersicht und deskriptive Analyse

Schwellenwerte

internationale Analyse: 24 Länder nutzen explizite & implizite Schwellenwerte

Die Analyse der internationalen Praxis zeigt eine große Variation in der Anwendung von Schwellenwerten. Von den 39 untersuchten Ländern verwenden 24 Länder (62%) Schwellenwerte in ihren Entscheidungsprozessen, davon sind zwei Drittel europäische Länder. Es wird dabei zwischen expliziten und impliziten Schwellenwerten unterschieden: Sieben Länder, darunter Estland, England und Wales, Irland, Polen, die Slowakische Republik, Slowenien und Thailand, arbeiten mit expliziten Schwellenwerten, während 17 Länder implizite Schwellenwerte nutzen.

11 der 24 Länder haben eine Schwellenwert-Range bzw. multiple Basis-Schwellenwerte

Die Mehrheit der identifizierten Länder sind Länder mit hohen Einkommen. Bemerkenswert ist, dass elf der 24 Länder mit einem Schwellenwert entweder eine Schwellenwert-Range oder mindestens zwei Basis-Schwellenwerte verwenden. Beispielsweise hat Kanada unterschiedliche Schwellenwerte für onkologische und nicht-onkologische Interventionen, während Slowenien je nach Entscheidungsträger verschiedene Schwellenwerte verwendet.

unterschiedliche Methoden zur Schwellenwertbestimmung in verschiedenen Ländern; 50 % geben keine explizite Berechnungsmethode an

Die Methoden zur Bestimmung der Schwellenwerte variieren stark: Zwölf Länder legen ihre Berechnungsmethode offen, wovon neun Länder einen BIP-basierten Ansatz verwenden. Dieser reicht von einfachen bis zu dreifachen BIP-Werten – sogenannten BIP-Faktoren – pro qualitätskorrigiertem Lebensjahr (QALY). Drei Länder – Australien, Lettland und Spanien – nutzen empirische Methoden, während die restlichen zwölf Länder keine explizite Berechnungsmethode angeben.

Schwellenwerte zwischen € 4.000 & € 142.450 pro QALY

Die tatsächlichen Schwellenwerte variieren erheblich zwischen € 4.000 und € 50.000 pro QALY, wobei der durchschnittliche Basis-Schwellenwert ca. € 28.500 beträgt, mit einer Spanne von € 4.340 (Thailand) bis ~€ 53.900 (Slowakische Republik). Bei Ländern mit Schwellenwert-Ranges liegt der durchschnittliche obere Schwellenwert bei ~ € 54.200. Hierbei weist die USA mit ~€ 142.450 den höchsten Wert auf.

statistische Analyse der Zusammenhänge zwischen Schwellenwerten, BIP pro Kopf & Lebenserwartung

Die vertiefende statistische Analyse konzentriert sich auf die Zusammenhänge zwischen gesunder Lebenserwartung, Bruttoinlandsprodukt pro Kopf und Schwellenwerten in verschiedenen Gesundheitssystemen. Die Ergebnisse sollten aber nicht kausal verstanden werden, sondern einfache Assoziationen darstellen.

umgekehrt U-förmige Beziehung zwischen Schwellenwerten & gesunder Lebenserwartung → nicht-lineare Beziehung zwischen Schwellenwerten & Gesundheitsoutcomes

Zwischen gesunder Lebenserwartung und Schwellenwerten zeigt sich eine schwache, umgekehrt U-förmige Beziehung. Der Zusammenhang zwischen Schwellenwert und gesunder Lebenserwartung ist bis zu einem Maximum von 70 Jahren bei einem Schwellenwert von € 31.650 positiv und nimmt danach bei weiter steigendem Schwellenwert ab, was verschiedene Interpretationsmöglichkeiten zulässt. Beispielsweise könnte diese Beziehung darauf hindeuten, dass es einen optimalen Schwellenwert (etwa € 31.650 €) gibt, der die gesunde Lebenserwartung maximiert, und dann abnimmt, wenn der Schwellenwert entweder höher oder niedriger als dieser optimale Wert ist.

unterschiedliche Muster je nach Berechnungsmethode

Bei der Analyse nach verschiedenen Berechnungsmethoden ergeben sich unterschiedliche Muster: Für empirische Schwellenwerte lässt sich aufgrund der geringen Fallzahl keine klare Beziehung ableiten. Bei BIP-basierten Schwel-

lenwerten bleibt die umgekehrt U-förmige Struktur erkennbar. Für Länder ohne spezifische Berechnungsmethode zeigt sich folgendes Bild: je höher der Schwellenwert, umso höher die gesunde Lebenserwartung, allerdings mit abnehmender Rate.

Beziehung zwischen Schwellenwert und BIP pro Kopf variiert je nach Methode

Die Beziehung zwischen Schwellenwerten und BIP pro Kopf variiert je nach Methode. Bei BIP-basierten Schwellenwerten zeigt sich ein direkter Zusammenhang, wobei der „BIP-Faktor" eine wichtige Rolle spielt. Der BIP-Faktor schwächt den linearen 1:1 Zusammenhang zwischen BIP pro Kopf und Schwellenwert ab. Dies wird bei der Slowakei und Polen deutlich, die mit einem dreifachen BIP-Faktor deutlich höhere Schwellenwerte aufweisen. Ohne diese beiden Länder besteht eine starke Korrelation zwischen BIP pro Kopf und Schwellenwert.

spezifische Ländercharakteristika beeinflussen möglicherweise Schwellenwertvariation

Bei Ländern ohne spezifische Berechnungsmethode ist der Zusammenhang schwächer ausgeprägt. Die zunehmende Varianz der Schwellenwerte bei höherem BIP pro Kopf deutet darauf hin, dass möglicherweise andere Faktoren wie landesspezifische Präferenzen und sozioökonomische Aspekte eine wichtige Rolle spielen, besonders in Ländern mit höherem Einkommen.

Modifikatoren und zusätzliche Entscheidungskriterien

Länder berücksichtigen neben Schwellenwerten weitere Kriterien

Im Entscheidungsfindungsprozess zu Erstattungen berücksichtigen einige Länder neben der reinen Effizienzbetrachtung durch Schwellenwerte weitere Kriterien. Gesundheitsmaximierung und Effizienz sind nicht die einzigen Ziele von Entscheidungsträgern und spiegeln auch nicht unbedingt die gesellschaftlichen Präferenzen bei der Ressourcenverteilung wider.

→ Modifikatoren

Daher werden zusätzliche Kriterien, sogenannte Modifikatoren, berücksichtigt. Diese Modifikatoren können dabei auf zwei verschiedene Arten angewendet werden:

quantitative Modifikatoren & …

- Quantitative Modifikatoren bzw. Schwellenwert-Modifikatoren werden direkt in der gesundheitsökonomischen Evaluation berücksichtigt und beeinflussen die ICER oder den Schwellenwert.

… qualitative Modifikatoren

- Qualitative Modifikatoren bzw. entscheidungsrelevante Modifikatoren hingegen fließen in den deliberativen Entscheidungsprozess ein.

ergänzen bzw. ersetzen Schwellenwerte im ganzen Entscheidungsprozess

Der Grundgedanke bei quantitativen Modifikatoren ist, dass gesundheitliche Verbesserungen für bestimmte Bevölkerungsgruppen oder spezifische Gesundheitsinterventionen monetär unterschiedlich bewertet werden. Qualitative Modifikatoren hingegen ergänzen die rein gesundheitsökonomischen Überlegungen in der Gesamtabwägung von Kriterien im Entscheidungsprozess.

15 der 24 Länder (63 %) verwenden Modifikatoren

Von den 24 untersuchten Ländern verwenden 15 Länder (63%) solche Modifikatoren. Zwölf Länder nutzen quantitative Modifikatoren, die den Schwellenwert oder die ICER erhöhen, wobei die konkrete Ausgestaltung sehr heterogen ist. Sechs Länder haben offiziell festgelegte qualitative Modifikatoren, und drei Länder verwenden beide Arten von Modifikatoren.

10 Modifikationskriterien

Insgesamt wurden zehn verschiedene Modifikationskriterien identifiziert:

- Schweregrad der Erkrankung (einschließlich End-of-Life-Behandlungen)
- Seltene Erkrankungen
- Allgemeine Gerechtigkeitsaspekte
- Spezifische Indikationen und Krankheiten
- Verfügbarkeit therapeutischer Alternativen

- Budgetauswirkungen
- Unsicherheit der ICER
- Innovationsfaktor
- Hocheffektive Einzeltherapien
- Relevanz für die öffentliche Gesundheit

häufig verwendete Kriterien: Schweregrad seltene Erkrankungen, Gerechtigkeitsaspekte, spezifische Indikationen & Verfügbarkeit von Therapiealternativen

Die am häufigsten verwendeten Kriterien sind der Schweregrad der Erkrankung und seltene Erkrankungen, gefolgt von allgemeinen Gerechtigkeitsaspekten, spezifischen Indikationen und der Verfügbarkeit von Therapiealternativen. Während quantitative Modifikatoren hauptsächlich bei vier Kriterien zum Einsatz kommen (Schweregrad, seltene Erkrankungen, spezifische Indikationen und Einzeltherapien), werden qualitative Modifikatoren bei fast allen Kriterien angewendet.

Diskussion und Implikationen für Österreich

HEE bisher untergeordnete Rolle im österreichischen Gesundheitswesen

Im österreichischen Gesundheitssystem spielen gesundheitsökonomische Evaluationen bisher eine untergeordnete Rolle und sind nur in bestimmten Fällen formal erforderlich, hauptsächlich bei der Bewertung von Arzneimitteln im ambulanten Bereich. Dabei müssen „pharmakoökonomische" Studien vorgelegt werden, wenn der Hersteller einen wesentlichen zusätzlichen Nutzen nachweisen will oder keine Behandlungsalternativen existieren. Mit dem kürzlich verabschiedeten Gesetz zur Bewertung von Krankenhausarzneimitteln und solchen an der Schnittstelle zwischen stationärem und ambulantem Sektor könnten gesundheitsökonomische Evaluationen in Zukunft eine stärkere Rolle spielen. Das Konzept der Schwellenwerte wurde jedoch bisher für keinen Entscheidungsprozess diskutiert.

Effizienz/Wirtschaftlichkeit rechtlich verankert, aber selten konkret operationalisiert

Zwar ist der Effizienzbegriff bzw. „Wirtschaftlichkeit" in verschiedenen Rechtsvorschriften verankert, wird aber selten konkret operationalisiert. Die wichtigsten gesetzlichen Grundlagen sind:

- Das Allgemeine Sozialversicherungsgesetz (ASVG) regelt die Verantwortung für die Sozialversicherung und enthält das „Wirtschaftlichkeitsgebot" in §133.
- Das Krankenanstalten- und Kuranstaltengesetz (KAKuG) bestimmt die Krankenhausversorgung und behandelt Effizienzaspekte bei der Arzneimittelbeschaffung sowie bei der Bewertung von „hochpreisigen und spezialisierten" Medikamenten in § 19 (4) und §62e (4).
- Das Bundesgesetz zur Qualität von Gesundheitsleistungen definiert Effizienzaspekte im Kontext von Gesundheitsleistungen.
- Die 15a B-VG Zielsteuerung-Gesundheit begründet den Einsatz von Instrumenten zur Steigerung der Effektivität und Effizienz mit der Verantwortung für den effizienten Einsatz von Steuern und Beiträgen.
- Das Bundesfinanzgesetz verweist auf das Wirtschaftlichkeitsprinzip im Kontext der nachhaltigen Gesundheitsversorgung.

stärkere Formalisierung & Operationalisierung von gesundheitsökonomischen Methoden in Österreich notwendig

→ erhöht Transparenz

Eine stärkere Formalisierung und Operationalisierung des Effizienzbegriffs und der dazu heranzuziehenden Methoden in Entscheidungsprozessen könnten hier zu Verbesserungen der Entscheidungstransparenz führen. Für eine standardisierte und vermehrte Anwendung gesundheitsökonomischer Evaluationen (in Kombination mit Schwellenwerten) in Österreich sind grundsätzliche Entscheidungen erforderlich: Zunächst muss geklärt werden, welche Rolle gesundheitsökonomische Evaluationen künftig spielen sollen. Darauf aufbauend sind Entscheidungen zur methodischen Ausgestaltung, zur Art der

Schwellenwertbestimmung und zur Integration zusätzlicher Entscheidungskriterien im Sinne von Modifikatoren zu treffen (Entscheidungsalgorithmus siehe Figure 1).

notwendige Maßnahmen

Zudem sind für eine systematischere Nutzung gesundheitsökonomischer Evaluationen mehrere Maßnahmen nötig:

- Erstellung detaillierter methodischer Richtlinien
- Entwicklung von adäquaten Methoden zur Bewertung von Kosten- und Nutzenparametern (Unit-Cost-Katalog/-Datenbank)
- Aufbau von Expertise, Schulung von Personal und Entscheidungsträgern
- Definition von Bewertungskriterien und transparenten Prozessen
- Harmonisierung der rechtlichen Begriffe mit wissenschaftlichen Standardbegriffen

proaktive Aufklärungsstrategie empfohlen:

Rationalisierung vs. Rationierung

Die Implementierung systematischer gesundheitsökonomischer Evaluationen inklusive Operationalisierung eines Schwellenwerts wird vermutlich kontrovers diskutiert werden, da solche Maßnahmen oft als „Rationierungsmaßnahmen" aufgefasst werden. Daher wird eine proaktive Aufklärungsstrategie empfohlen, die den Unterschied zwischen Kostendämpfung (Rationierung) und effizienter Ressourcennutzung (Rationalisierung) verdeutlicht und die Vorteile transparenter Entscheidungsprozesse aufzeigt.

Limitationen und Forschungsbedarf

Länderselektion nicht systematisch

manuelle Literaturrecherche

Der vorliegende Bericht weist verschiedene methodische Limitationen auf. Die Länderauswahl basiert nicht auf einer vollständigen systematischen Erhebung, sondern konzentriert sich auf europäische Länder und solche mit Ähnlichkeiten zum österreichischen Gesundheitssystem. Die Literaturrecherche wurde manuell durchgeführt mit Fokus auf die tatsächliche Entscheidungspraxis.

Kategorisierung der Modifikatoren nicht immer eindeutig

Die Kategorisierung der Modifikatoren ist nicht immer eindeutig möglich, da es Überschneidungen zwischen verschiedenen Kriterien gibt. Zudem wurde auf eine Kaufkraftbereinigung der Schwellenwerte (Purchasing Power Parities/PPP) verzichtet, da konventionelle PPP-Anpassungen möglicherweise nicht adäquat sind für die spezifischen Charakteristika der verschiedenen Länder.

deskriptive Analyse gibt erste Hinweise, kann komplexe Schwellenwert-Zusammenhänge aber nicht vollständig erklären → weitere Forschung notwendig

Die durchgeführte deskriptive Analyse gibt zwar erste Hinweise auf mögliche Zusammenhänge zwischen Schwellenwerten, BIP pro Kopf und gesunder Lebenserwartung, kann aber die komplexen Beziehungen zwischen den untersuchten Variablen nicht vollständig erklären. Weitere Forschung unter Einbeziehung komplexerer Modelle und zusätzlicher Faktoren wie landesspezifischer Besonderheiten ist daher erforderlich.

Conclusio

Berücksichtigung von Effizienz bei Entscheidungen ethisch notwendig

Die Berücksichtigung von Effizienzkriterien bei Erstattungsentscheidungen stellt eine ethische Notwendigkeit im Umgang mit öffentlichen Ressourcen dar. Die zentrale Herausforderung liegt dabei nicht in der Frage ob, sondern wie Effizienzbetrachtungen und mögliche Modifikatoren konsistent und transparent in Erstattungsprozesse integriert werden können.

kein „Goldstandard" für Implementierung von Schwellenwerten → jeder Ansatz hat Vor- & Nachteile

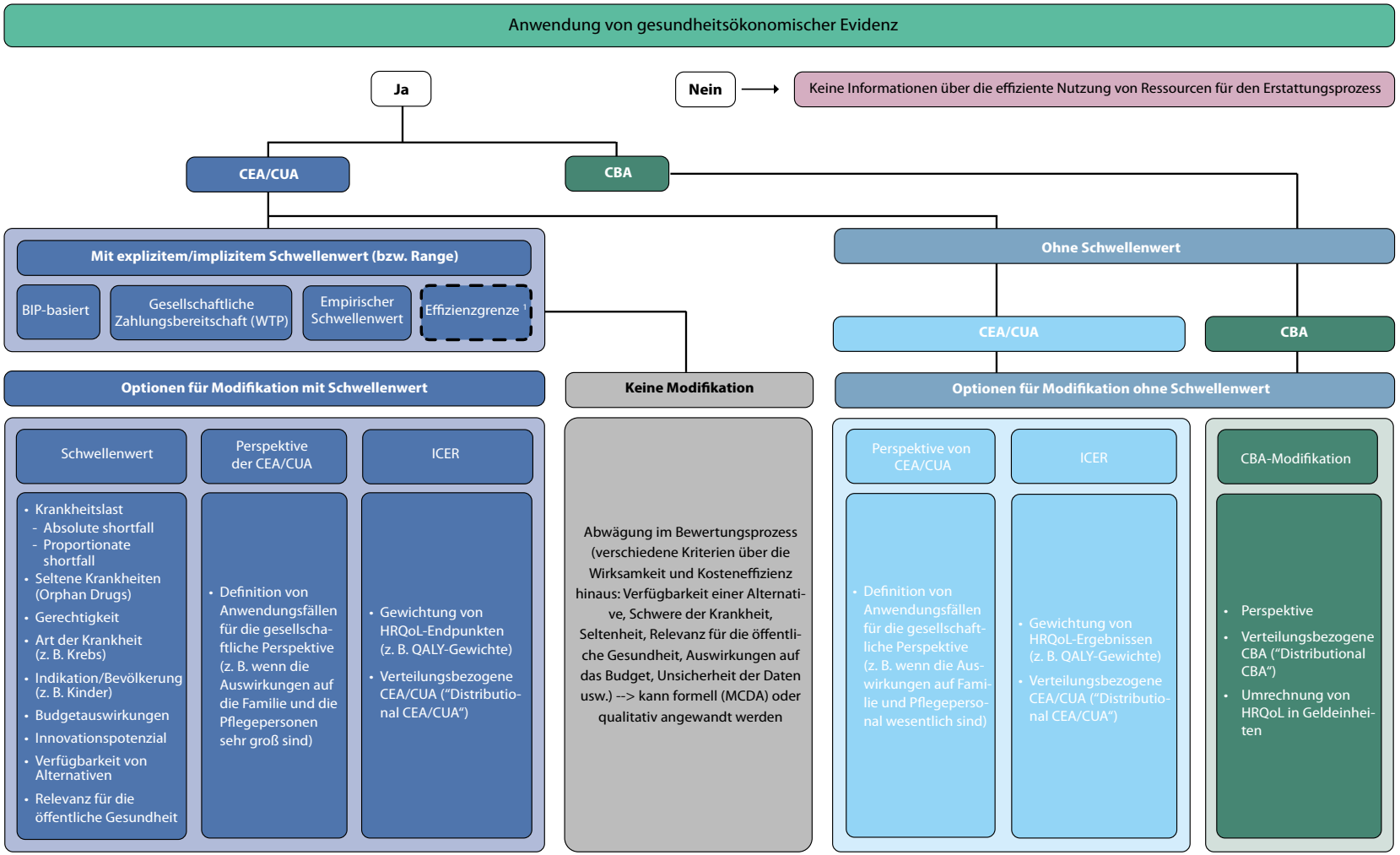
Die internationale Erfahrung zeigt, dass es keinen universellen „Goldstandard" für die Implementierung von Schwellenwerten gibt. Jeder methodische Ansatz weist spezifische Vor- und Nachteile auf und muss an den nationalen Kontext angepasst werden. Dabei ist zu beachten, dass keine der Methoden wertneutral ist – alle basieren auf ethischen und gerechtigkeitsbezogenen Grundannahmen.

Maßnahmen: Forschung, Sensibilisierung relevanter Akteure, Aufbau von Expertise & Kapazitäten, kontinuierliche Evaluation & Anpassung

Für eine erfolgreiche Implementierung in Österreich sind verschiedene begleitende Maßnahmen erforderlich. Dazu gehören weitere Forschung zu methodischen Aspekten, die Sensibilisierung der relevanten Akteur*innen und der Aufbau entsprechender Expertise und Kapazitäten. Auch die Entwicklung transparenter Entscheidungsprozesse und deren kontinuierliche Evaluation und Anpassung sind von zentraler Bedeutung.

konkrete Ausgestaltung erfordert politische Entscheidung unter sorgfältiger Abwägung der Vor- & Nachteile

Die vorliegende Evidenz zeigt, dass die Implementation von Schwellenwerten zwar ein komplexer Prozess ist, der aber zu mehr Transparenz und Effizienz im Gesundheitssystem beitragen kann. Die endgültige Entscheidung über die konkrete Ausgestaltung muss dabei auf politischer Ebene getroffen werden, wobei die verschiedenen methodischen Optionen und ihre Implikationen sorgfältig abgewogen werden sollten.



[1] *Effizienzgrenzen-Ansatz (EFA): Bei der EFA gibt es keinen expliziten ICER-Schwellenwert, sondern eine Preisobergrenze. Daher gelten die Modifikationsoptionen nur teilweise für die EFA.*

Abkürzungen: *CBA … Cost-Benefit-Analysis, CCA … Cost-Consequences-Analysis, CEA … Cost-Effectiveness Analysis, CUA … Cost-Utility-Analysis, GDP … Gross Domestic Product, HRQoL … Health Related Quality of Life, HTA … Health Technology Assessment, ICER … Incremental Cost-Effectiveness Ratio, MCDA … Multi-Criteria Decision-Analysis, QALY … Quality-Adjusted Life Years, WTP … Willingness-to-Pay*

Figure 1: Entscheidungsalgorithmus für die Verwendung gesundheitsökonomischer Evidenz in Kombination mit oder ohne Schwellenwerten

1 Introduction

1.1 General Background

gesundheitsökonomische Evaluation (HEE) integraler Bestandteil von Erstattungsentscheidungen in einigen Staaten

In several countries, Health Technology Assessment (HTA) is integral to reimbursement decisions and funding recommendations for healthcare interventions [1, 2]. In addition to effectiveness assessment and analysis of other (e.g., ethical, organisational, social) aspects, health economic evaluation (HEE) is a pillar of textbook HTA.

zunehmender Einsatz aufgrund von:

Arguments for the increasing use of HEE given in the literature or raised by decision and policy makers are manyfold and include, among others:

- Importance of priority setting due to rising costs of health care associated with new technologies, costly innovations, and changing demographics. — **Priorisierung von Handlungsalternativen**
- Scarcity of financial means or finite nature of resources, while demand for health or health care services and needs are allegedly infinite. — **Verknappung von Ressourcen**
- Avoidance of budgetary imbalances. — **Sicherstellung eines "nachhaltigen" Budgets**
- Assuring budgetary sustainability.
- Rational and efficient use of taxpayer money. — **rationaler Ressourceneinsatz**

primäres Ziel von HEE: Informationsgrundlage für den effizienten Ressourceneinsatz bereitstellen

Although HEEs rest on strong assumptions and many of these arguments need further contextualisation, the usefulness of health economic methods for planning in the healthcare system cannot be denied. The primary purpose of HEEs, such as cost-effectiveness analyses (CEA), is to inform decision and policy makers of the efficient use of resources in the healthcare system or, in simple terms, costs of an intervention are minimised, and benefits are maximised [3, 4]. Still, "textbook-like" HEE is not necessarily conducted in every country using HTAs for decision-making as the application of HEEs seems to depend on social values and the institutional context in the respective jurisdiction [5, 6].

Schwellenwert zentral, um effizienten Ressourceneinsatz darzustellen → aber mit Limitationen verbunden

HEE's explanatory power regarding efficiency is only given if the output magnitude, i.e. the additional costs per additional unit of health effect when comparing two interventions[1], is compared with a reference value – the incremental cost-effectiveness (ICER) threshold[2]. While HEE combined with ICER thresholds can support decisions, applying HEEs as a policy tool has several limitations because of the weaknesses of the ICERs and the associated threshold.

[1] The result of this comparison is a ratio called incremental cost-effectiveness ratio (ICER). The health economic literature states that this ratio represents the economic value of an intervention compared with an alternative (comparator).

[2] *"The cost-effectiveness threshold is the maximum* (money) *amount a decision-maker is willing to pay for a unit of health outcome. If the cost-effectiveness (ICER) of a new therapy (compared with a relevant alternative) is estimated to be below the threshold, then (other things being equal) it is likely that the decision-maker will recommend the new therapy."* [7] (https://yhec.co.uk/glossary/cost-effectiveness-threshold/)

Firstly, no universal ICER threshold exists. There are several methods for deriving threshold values [8-11]. However, each approach has its methodological limitations. Very few jurisdictions define an explicit threshold [1, 4, 12]. Even jurisdictions that apply explicit thresholds, such as the National Health Service (NHS) in the United Kingdom, use a threshold range for its funding decisions [13].

kein universeller Schwellenwert, aber mehrere Ansätze zur Kalkulation existieren

In addition, the ICER threshold value is based on several strong methodological assumptions resting on neoclassical (extra-)welfarist theory. Neoclassical welfarist and extra-welfarist theory, in turn, are based on the philosophical theory of utilitarianism. A HEE only gives information on the optimal use of resources in an economic sense, meaning whether resources are used efficiently under a politically fixed budget. Health maximisation is not the only aim of decision and policy makers, and efficient use of resources is not necessarily the same as getting the highest value for money, "being worthwhile", or affordable [14]. Decision and policy makers also consider criteria such as equity, equal access, or public preferences in their political decisions. These criteria – so-called modifiers – are commonly not explicitly covered within a standard HEE and the ICER threshold. Hence, some countries use further factors in decision-making or extend their HEE with specific quantitative or qualitative modifiers [1].

Schwellenwert & Bewertung der Effizienz basiert auf starken methodologischen Annahmen (Neoklassische Theorie/Utilitarismus)

bspw. ist Gesundheitsmaximierung nicht das einzige Ziel von Entscheidungsträgern

These modifiers relevant to decision-making and HEE vary across healthcare systems. They can potentially include the severity of illness (disease burden, disease category, end-of-life related), rarity of the disease (orphan disease), equity and equality of healthcare access, or availability of alternatives [1]. Even though explicit thresholds guarantee transparency and some consistency in the decision-making process, the ICERs and associated thresholds' weaknesses need consideration when being used as a policy-making tool.

einige Staaten verwenden Modifikatoren bei Entscheidungen (seltene Erkrankung, „fairer" Zugang zur Versorgung, Krankheitslast, etc.)

Therefore, in some countries, HEE is not included in the decision-making process, as these countries seemingly do not place as much emphasis on efficient resource allocation. Some countries use HEEs but do or do not have explicit thresholds, and others use thresholds but also employ modifiers in the decision-making process [1].

verschiedene Zugangsweisen in unterschiedlichen Ländern

1.2 Problem Statement and Rationale of the Project

In Austria, HEE has so far played a minor role in reimbursement decisions, and an ICER threshold has not yet been defined or discussed [15]. However, against the backdrop of challenges in achieving a sustainable public health system and introducing thresholds in many European countries, it is crucial to understand the principle of thresholds in the context of the Austrian healthcare system and to analyse the benefits and limitations of thresholds in Austria.

Problemstellung: HEE spielen in Österreich (AT) eine untergeordnete Rolle → Bedeutung gesundheitsökonomischer (ges.ök.) Konzepte im AT Kontext?

1.3 Project Objectives and Research Questions

Objectives

The project aims to explain the theoretical foundations, purpose, and implications of ICER threshold values used in HEE. A critical review of important health economic concepts for decision-making and a discussion of the implications are required to achieve these goals.

Ziele des Berichts: Erklärung theoretischer Grundlagen & kritische Analyse ges.ök. Konzepte

Moreover, the project aims to provide an overview of the countries that use HEE with associated ICER thresholds as part of reimbursement decisions and funding recommendations. We identify values and further factors (modifiers) used instead of or in addition to explicit ICER thresholds in HEEs in HTAs and the decision-making process. The underlying methods, values and rationales that determine the differences in thresholds and modifiers across countries and health systems are described.

Länderübersicht von Schwellenwerten, Modifikatoren & entscheidungsrelevanten Faktoren

In a final step, we put the findings into the context of the Austrian healthcare system, aiming to improve understanding of what the implementation of a threshold would mean in the decision-making processes and which activities would be required for defining and implementing a threshold in Austria.

Einbettung Ergebnisse in AT Kontext & Diskussion Schwellenwert-Implementierung in AT

Non-Objective

The report …

- does not provide an assessment of the Austrian legal framework concerning HEE and the consequences of applying ICER thresholds or other decision factors (modifiers) in the decision-making process in the form of a legal report.

Nicht-Ziel: juristisches Gutachten einer Schwellenwert-Implementierung

Research Questions

The following research questions (RQ) will be answered in the course of the report:

4 Forschungsfragen (FF):

FF1 What are the theoretical foundations and implications of ICER thresholds and their relevance for the decision-making process?

theoretische Grundlagen?

FF2 What are possible methods to define thresholds and their advantages and limitations?

Methoden zur Schwellenwertkalkulation?

FF3 Which countries employ ICER thresholds in their HEE, and which other factors play an essential role in HEE in HTAs and decision-making?

Länder mit Schwellenwerten & Modifikatoren?

FF4 What role do efficiency considerations play in Austrian healthcare decision-making and reimbursement processes? How are efficiency aspects addressed in relevant laws? What is the current state of health economic evaluations in Austria, and which necessary activities would a threshold implementation involve?[3]

Bedeutung von Effizienzüberlegungen & Schwellenwerten für AT?

[3] This question also encompasses the identification of decision-making contexts that would be affected by introducing such thresholds.

2 Methodology

2.1 Overview of the Report and PICo Analysis

Bericht basiert auf Literaturübersicht & empirischer Analyse

The following report is based on a review of the literature (empirical and theoretical), policy documents, guidelines from a range of countries, and expert knowledge. Furthermore, an empirical analysis of identified thresholds and modifiers was conducted.

schrittweise Vorgehensweise:

The following steps were conducted:

- **Übersicht der Literatur** Overview of the literature and theoretical foundations of health economic thinking including health economic evaluations (Chapter 3).
- **Länder- & Schwellenwertübersicht** Identification and overview of countries with thresholds, modifiers, and description of their HEE methods used in the reimbursement process (Chapter 4).
- **empirische Analyse** Empirical analysis of the thresholds and modifiers (Chapter 4).
- **Einbettung in AT Kontext** Review of the results and contextualisation of the findings for the Austria healthcare system (Chapter 5).
- **Zusammenfassung & kritische Reflexion** Summary and critical reflection of the findings (Chapter 6).

Vorgehensweise durch Problem, Interesse, Kontext (PIKo)-Schema geleitet

The following Problem, Interest, and Context (PICo) scheme (see Table 2-1) guided the report, from identifying the relevant literature to identifying information of thresholds to elaborate all four research questions.

Table 2-1: PICo analysis

Problem	HEE plays a minor role in reimbursement decisions in Austria, and an ICER threshold has not yet been defined or discussed. There is currently a lack of knowledge on HEE's advantages, methodological challenges, and strengths and weaknesses in ICER thresholds in decision-making in the Austrian context. Decision makers and policy makers need methodological guidance when making decisions on criteria to be used for reimbursement or funding decisions.
Interests	■ **RQ1 and RQ2:** Understanding the theoretical foundations, purpose, and implications of ICER thresholds and modifiers in HEE and HTAs. Methods for deriving ICER thresholds are elaborated, and identified information will be critically discussed. ■ **RQ3:** Learning how thresholds and modifiers are used in other countries. ■ **RQ4:** Understanding the pros and cons of thresholds in the Austrian healthcare system context and implementation requirements (legal regulations, necessity of a legal report or regulatory impact assessment, methodical approach for deriving thresholds, involvement of researchers, general implementation aspects, etc.). *Not of interest: Legal analysis of HEE and associated ICER thresholds in the Austrian healthcare context.*
Context	International healthcare context with a focus on European countries and countries with similarities in the healthcare system.
Language	English/German
Publication Type	All types of publications

Abbreviations: HEE … Health Economic Evaluation, ICER … Incremental Cost-Effectiveness Ratio, PICo … Problem, Interests, Context

2.2 Theoretical Foundations of Health Economic Evaluations and Methods to Define ICER Thresholds

Vorgehensweise FF 1 & 2

To answer research questions 1 and 2, we give an overview of the theoretical foundations, purpose, and implications of ICER thresholds and modifiers in HEE and HTAs. This task included the following steps:

- **Übersicht grundlegender ges.ök. Konzepte & Definitionen (Def.)**
  Overview of basic concepts, definitions, the applied methodology and its critical reflection in HEE based on the relevant literature (textbooks and method papers). The literature is identified on the authors' knowledge and supported by a snowballing strategy.
- **kritische Reflexion**
  Critical discussion on the methodology and logic of HEE and implications for decision-making.
- **Literaturübersicht der Schwellenwert-Kalkulationsmethoden**
  Literature review on methods to derive a threshold and classification according to categories identified alongside the analysis process.

2.3 Search for Information on Thresholds and Overview of Countries

FF 3: 5 Publikationen als Startpunkt zur Länderidentifikation

To answer research question 3, we provide an overview of countries that use HEE with thresholds and/or modifiers. As a starting point, we used the following publications to identify countries with established thresholds:

Table 2-2: Relevant publications as a starting point

Publication by	Year	Publication name
Zhang and Garau [2020]	2020	International cost-effectiveness thresholds and modifiers for HTA decision-making
Santos et al. [2018]	2018	Cost-effectiveness thresholds: Methods for setting and examples from around the world
Cameron et al. [2018]	2018	On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review
Schwarzer et al. [2015]	2015	Systematic overview of cost-effectiveness thresholds in ten countries across four continents
Cleemput et al. [2008]	2008	Threshold values for cost-effectiveness in health care

One common scope of all five publications was to identify countries with established thresholds.

Durchsicht von ges.ök. Leitlinien (LL)

Secondly, we searched through the "Overview of Pharmacoeconomic Guidelines around the World" by the Professional Society for Health Economics and Outcomes Research (ISPOR) (https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines/pe-guideline-detail) [18]. The following search strategy was used to identify the countries and the relevant information on thresholds in country guidelines:

Table 2-3: Search strategy and identification of information on thresholds in country guidelines

Guidelines in English and German language:
The identified health economic guidelines and/or health economic sections in HTA guidelines in English or German language were searched for thresholds using the following search terms: ■ Threshold/Schwellenwert ■ ICER ■ Evaluate, Evaluation ■ Gross domestic product (GDP) ■ Economic*/Gesundheitsökonom*
Non-English and non-German language guidelines
In the case of non-English or non-German guidelines, the following English search terms were translated to the specific guideline language and guidelines were subsequently searched with the translated search terms: ■ Threshold ■ Evaluation ■ Gross domestic product (GDP) ■ Economic*

GDP … Gross Domestic Product, HTA … Health Technology Assessment, ICER … Incremental Cost-Effectiveness Ratio

gezielte Literaturrecherche zu Schwellenwerten in 1 gesundheits-wissenschaftlichen Datenbank & 2 Suchmaschinen

Furthermore, a targeted literature search for threshold information, HTA and pharmacoeconomic guidelines for the identified countries was conducted via

- Google Search.
- Google Scholar.
- Medline (via PubMed: https://pubmed.ncbi.nlm.nih.gov/).

The following search strategy was used during this step:

Table 2-4: Search strategy for the targeted hand search

Search term	**linked with (AND)**	**linked with (OR/AND)**	**Suchbegriff**	**verknüpft mit (AND)**	**verknüpft mit (OR/AND)**
English terms			**Deutsche Begriffe (German terms)**		
identified countries (e.g., Ireland)	ICER* CET* WTP* HTA* health economic	threshold threshold guideline guideline	**identifiziertes Land (z. B. Irland)**	IKEV* IKNV*	Schwellenwert Schwellenwert

* *Spelled in full terms were also searched*

Abbreviations: CET … Cost-effectiveness threshold, HTA … Health technology assessment, ICER … Incremental cost-effectiveness ratio, IKEV … Inkrementelles Kosten-Effektivitäts-Verhältnis, IKNV … Inkrementelles Kosten-Nutzwert-Verhältnis, WTP … Willingness to pay

2.4 Country Selection, Extracted Information, Country Overview, and Analysis

2.4.1 Country Selection and Extracted Information

Fokus: Länder aus zugrundeliegenden Publikationen, europäische Länder & Publikationen/LL aus gezielter Handsuche

The starting point for selecting relevant countries were the identified publications and the ISPOR guideline overview, with a focus on European countries and countries with similarities in the healthcare or social insurance systems to Austria. Further publications identified through the targeted hand search were also included. Only countries with thresholds expressed as cost per additional quality-adjusted life year (QALY), life-year gained (LYG), and disability-adjusted life year (DALY) were considered.

Datenextraktionstabellen erstellt & Extraktion von relevanten Informationen

We prepared a data extraction table for all identified countries. Non-English language sources were translated using DeepL (www.deepl.com), Google Translate (https://translate.google.com/), and subsequently extracted.

The following information was extracted from the identified literature and tabulated:

Table 2-5: Extracted information from identified guidelines and publications

Countries with ICER thresholds	

■ Country
■ Type of healthcare system
■ Threshold (local currency)
■ Currency (Abbreviation)
■ Threshold EUR (2022)
■ Underlying calculation method
■ Constant (2015) gross domestic product (GDP) per capita (2022)
	■ Healthy life expectancy at birth (2022)
	■ Key information in HEE guideline
	  ▪ Outcome measures specified in guideline/HEE
	  ▪ Threshold in guideline (Yes/No/Other)
	  ▪ Guideline type
	■ Notes (Implicit/Explicit threshold)
	■ Sources

Countries with ICER or threshold modifiers (quantitative modifiers) and/or decision modifiers (qualitative modifiers)	
■ Country ■ Quantitative modifiers ■ Threshold (local currency) ■ Currency	■ Threshold EUR (2022) ■ Qualitative modifiers ■ Other characteristics and notes ■ Sources

Abbreviations: ICER … Incremental Cost-Effectiveness Ratio

Klassifikation der verschiedenen Gesundheitssysteme nach European Observatory on Health Systems & Policies

Information to classify the different healthcare systems was mainly taken from the European Observatory on Health Systems and Policies [19], Ferreira et al. [2018], and the International Health Care System Profiles by the Commonwealth Fund [21], and was verified by further sources.

Healthcare systems can be classified into four basic models according to the references above:

Beveridge-Modell: finanziert durch Steuern

- *Beveridge model (Universal healthcare model):* The government is responsible for funding and providing healthcare services. The raised budget consists exclusively of tax payments.

Bismarck-System: "Sozialversicherungs-modell"

- *Bismarck model (Social security model):* Employers and employees pay into a single public fund through payroll deductions. A self-governing body usually controls this public fund, with the government supervising.

- *National health insurance model (NHIM):* The government is the single-payer for all health services and collects financial means through a state-operated insurance scheme into which every citizen pays. It is a combination of the Beveridge and Bismarck model.
- *Out-of-pocket model:* Individuals pay for their own care directly without an insurance system.

nationales Krankenversicherungs-modell (NHIM)

Out-of-Pocket-Modell

Some countries cannot be assigned to one of the four basic models and combine various characteristics of them (mixed models). Furthermore, some healthcare systems, such as those in Eastern Europe, are in transition.

Mischsysteme & Übergangsmodelle

Data on the type of product to which the threshold applies, whether it is a medicinal drug, medical device, or general health care intervention, were taken from guidelines and identified publications. Like the information on the healthcare system, this information is only indicative, as the available information is incomplete.

Infos zu Art des medizinischen Produkts nur indikativ

Information on threshold values and modifiers was taken from the identified literature. Each publication reported in the five overview studies (Table 2-2) was checked for valid threshold information. The extraction tables also list the underlying method for calculating the threshold and information on whether the threshold is set implicitly or explicitly in the particular jurisdiction.

Schwellenwerte des jeweiligen Landes & zugrundeliegende Kalkulationsmethoden extrahiert

We define explicit health economic thresholds as thresholds or threshold ranges defined in an official document by a public authority or those set legally. Health economic thresholds mentioned in guidelines or thresholds reported in identified publications that may be used as guidance, or "rule of thumb" are defined as implicit (informal) thresholds. These explicit and implicit thresholds are listed in the main cell of the table. Thresholds for countries that were estimated in separate scientific publications and neither explicitly nor implicitly play a role in HEE or the decision-making process are listed in the footnotes of the tables in the Appendix (Table A-1 and Table A-2).

Unterscheidung zwischen expliziten/offiziellen & impliziten/informellen Schwellenwerten; zusätzlich: Auflistung von Schwellenwerten aus wissenschaftlichen Publikationen

For the modifiers, we used the following criteria grouping:

Gruppierung der Modifikatoren nach 10 Kategorien/Kriterien

- Severity of disease including end-of-life treatments.
- Rare diseases (Orphan diseases).
- Equity.
- Specific indications and diseases (e.g. non-orphan diseases in oncology, paediatric indications).
- Availability of therapeutic alternatives/unmet needs.
- Budget impact.
- Uncertainty of ICER/Overall confidence in the effect.
- Innovation factor.
- High-impact single and short-term therapies (SSTs)
- Public health relevance.

To maintain precision and avoid double counting, we assigned countries with specific modifiers to single criterion groups where possible, though in some cases, a one-to-one correspondence could not be achieved.

wenn möglich, dann klare Zuweisung der Kriterien zu Kategorien

We subdivided the modifiers into threshold modifiers (quantitative or threshold-modifying criteria) and decision modifiers (qualitative or decision-modifying criteria). Quantitative modifiers are already considered in the HEE and alter the applied threshold amount. Qualitative modifiers are decision crite-

Unterscheidung zwischen quantitativen (quant.) Schwellenwert- bzw. ICER-Modifikatoren …

ria intended to supplement health, economic and efficiency considerations in decision-making. A more in-depth explanation of the differences is given in Chapters 3.5 and 4.2.1. The adjusted thresholds were also tabulated in the extraction tables.

… & qualitativen (qual.) Entscheidungs-modifikatoren

Additionally, we present whether an identified country has a guideline, the guideline type[4], and information on whether the threshold is reported. Furthermore, other characteristics and notes on the assessment and reimbursement process were extracted for selected countries with modifiers.

bspw. relevante Infos aus LL extrahiert

The full data extraction tables, including the sources of information for each country, can be found in Table A-1 and Table A-2 in the Appendix.

alle Daten & Infos in Tabellen im Appendix

2.4.2 Country Overview and Analysis

Data sources and Adjustments

Information on the constant (2015) gross domestic product (GDP[5]) per capita in US dollars (USD) for the year 2022 was taken from the World Bank Online Database [22] (https://databank.worldbank.org/). We included healthy life expectancy (HLE) to depict a proxy of health differences and longevity between countries. Data on HLE at birth was sourced from the World Health Organisation (WHO) database [23] (https://www.who.int/data/gho/data/indicators/indicators-index). The most recent HLE data is from the year 2021.

Daten zu Bruttoinlandsprodukt (BIP) & Healthy Life Years (HLE) von Weltbank & Weltgesundheits-organisation (WHO)

The United Kingdom (UK) GDP and HLE data were used for both Scotland and England/Wales. Taiwan's GDP and HLE data were taken from various sources as the data was not available in the databases used. The data on Taiwan's GDP was taken from the International Monetary Fund (IMF), but the data on the GDP per capita for the year 2022 was only available at current prices [24]. The HLE data at birth was taken from a publication estimating the HLE at birth for the year 2017 from the Taiwan national health insurance database [25].

weitere Quellen: internationaler Währungsfonds (IMF) & weitere Publikationen

[4] The taxonomy of the guideline type is according to the ISPOR definition: Pharmacoeconomic recommendations (PER) are country-specific economic evaluation guidelines or recommendations published by experts in the field but are not "officially" recognized or required by the healthcare decision-making bodies/entities in this country/region for reimbursement. PE Guidelines (PER) are country-specific "official" guidelines or policies concerning economic evaluation that are recognized or required by the healthcare decision-making bodies/entities in this country/region for reimbursement. Submission Guidelines (SubG) are country-specific "official" guidelines or policies concerning drug submission requirements with an economic evaluation part/section and are required by the healthcare decision-making bodies/entities in this country/region for reimbursement [18]. For countries that are not listed in the ISPOR overview, the classification was conducted by the authors based on the available information in the specific guideline.

[5] "*GDP per capita is gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in constant 2015 U.S. dollars*" – The World Bank [2024]. The GDP at constant prices has the advantage to adjust for the effects of price inflation by using a reference year as an anker.

zugrundeliegende BIP-Daten wurden adjustiert

weitere Kalkulationen & Umrechnungen (z. B. Fremdwährungen)

The GDP per capita for each country is presented in 2022 Euro (€) using the official exchange rate (Local Currency Unit per US$, period average) from the year 2022 by the World Bank. For countries that use thresholds on a GDP-basis (e.g. 1-3 x GDP) with no recent published data, we calculated the thresholds based on the constant (2015) GDP. The threshold for non-Euro area countries with no recently available threshold information in the particular local currency unit (LCU) was calculated by using the average exchange rate of the year 2022 from the European Central Bank (ECB) (https://www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/index.en.html) [26].

keine Inflationsanpassung, da rezente Daten verfügbar

We did not adjust for inflation for the identified non-GDP-based explicit and implicit thresholds as these thresholds are fixed for a specific time, and data on these thresholds were quite recent.

keine Anpassung der Kaufkraftparitäten (PPP), da Schwellenwerte keine Output-Daten sind & länderspezifische Präferenzen (Präf.) hinsichtlich eines Warenkorbs widerspiegeln

wird von Herstellern bei ihrer Preispolitik berücksichtigt

In the descriptive analysis for the GDP per capita and the thresholds, there was no adjustment for purchasing power parity (PPP), i.e., accounting for different relative costs of goods and services across countries. The rationale for this approach is that conventional PPP adjustment approaches may not be adequate. Furthermore, the countries' underlying consumer baskets (used to define PPP), including commodities and especially services, differ across countries. Currently applied thresholds are not an output measure such as GDP but rather reflect the specific jurisdiction's valuation and the production- or resource-related affordability given the jurisdictions' prices for health care interventions compared to other commodities and services. Both factors are also considered by pharmaceutical companies and manufacturers of medical devices when setting the maximum achievable prices in their product portfolio and in price negotiations with each jurisdiction.

keine PPP-angepassten Schwellenwerte anderer Staaten → begrenzter Informationswert für Entscheidungsträger in AT

In summary, the knowledge of PPP-adjusted information on other countries' thresholds has no added value for Austrian decision and policy makers. It is not relevant for them to know how much one € is worth in the Slovak Republic because this € is not spent in Slovakia at Slovakian prices. In our understanding, it is more informative to have a rough reference to the countries' actual threshold. For GDP-based thresholds, this is already given by the GDP factor, resulting in a specific threshold, e.g. threshold per QALY = 3 x GDP.

Limitation von nicht-PPP-angepassten Schwellenwerten:

absolute Schwellenwerte über Länder „theoretisch" nicht vergleichbar

A downside of not adjusting for PPP and only using market exchange rates is that GDP-based thresholds in countries with a lower GDP are underestimated. Typically, higher price levels can be observed in high-income countries (HICs), while lower-income countries have lower price levels (Balassa-Samuelson effect). Market exchange rate-based cross-country comparisons of GDP at its expenditure components reflect differences in economic outputs (volumes) and prices. Due to the difference in price levels, the size of higher-income countries is inflated, while the size of lower-income countries is deflated. A PPP adjustment of the GDP would reflect economic output differences ("differences in the real economy") as the adjustment controls for price level differences between the countries [22]. For example, the constant (2015) GDP per capita in € for the Slovak Republic in 2022 was € 17,953. The constant (2021) GDP per capita in USD adjusted for PPP in the same period was € 36,677 [22]. This difference is also reflected in the GDP-based thresholds. The non-PPP-adjusted GDP-based threshold (3 x GDP) in the Slovak Republic is € 53,860, and the adjusted threshold is € 110,031.

aus Transparenzgründen Angabe von PPP-angepassten Schwellenwerte im Appendix

For transparency reasons and to provide "complete" information, we list PPP-adjusted thresholds in the full extraction tables Table A-1 and Table A-2 in the Appendix. However, we did not use this data in the analysis. We list the constant (2021) GDP per capita PPP (adjusted for the year 2022) for jurisdictions using GDP-based thresholds. For jurisdictions using non-GDP-based thresholds, we adjusted the main explicit and implicit thresholds for PPP using the web-based Campbell & Cochrane Economics Methods Group (CCEMG) – Evidence for Policy and Practice Information and Co-ordinating (EPPI) Centre Cost Converter [27]. Thresholds listed in the footnotes of the tables in the Appendix that were estimated in separate scientific publications and neither explicitly nor implicitly play a role in the decision-making process in countries were also not adjusted for PPP.

Analytical Approach and Methods

stufenweise Darstellung & Analyse der Daten

We summarised and analysed the extracted information on the countries' threshold and modifier information in Chapters 4.1 and 4.2 according to the extraction categories. We proceeded as follows:

- **Länderübersicht & Schwellenwertübersicht**
  First, we gave a brief overview of the countries and general characteristics of the ICER thresholds. Furthermore, we summarised the collected variables (GDP per capita, HLE, ICER threshold data).
- **deskriptive Analyse der verschiedenen Daten**
  Zusammenhang Schwellenwerte, GDP & HLE
  grafische Darstellung, Korrelationsanalyse & Anpassungsgüte/ Bestimmtheitsmaß (R^2)
  In the second step, we descriptively analysed the thresholds across countries and the relation of ICER thresholds, the HLE at birth in years, and the GDP. The intention was to show whether there is a correlation between HLE in years and thresholds on the one hand and between GDP per capita and thresholds on the other. By analysing these relationships, we wanted to find out whether countries with a higher threshold also have a higher HLE. In addition, we wanted to find indications of whether governments in countries with a higher GDP are willing to spend more for additional health gains. As part of this analysis, we plotted the variables and fitted different linear regression models with linear and non-linear functional forms (polynomial and power function). Furthermore, we calculated correlations and goodness of fit measures (multiple R^2) of the regression models. We did not conduct inferential statistical tests for the two hypotheses. Therefore, the results need to be interpreted with caution. For the analysis, we used the R 4.4.1 open-source programming language (https://www.r-project.org/) with RStudio 2024.04.2 Build 764.
- **länderspezifische Charakteristika**
  In the third step, each country with an existing threshold is described separately in the form of country-profiles to highlight country-specific characteristics regarding the application of HEE and ICER thresholds.
- **Präsentation & Analyse der Modifikatoren gemäß Zhang & Garau [2020]**
  The Chapter on the modifiers (Chapter 4.2.2) follows the presentation format of the results as in Zhang and Garau [2020] and accordingly provides an updated overview of the modifiers frequently used in different jurisdictions.

2.5 Health Economic Evaluation in Austria and Discussion of Critical Factors for Implementing Thresholds

The last part of the report is based on expert knowledge. We proceeded according to the following three steps:

Einbettung in den AT Kontext

- In In the first step (Chapter 5.1), we conducted a hand search for decision-relevant documents, such as legal texts or system descriptions that mention efficiency ("*Wirtschaftlichkeit*") and other health-economic-relevant terms. The summary of the laws outlined in Chapter 5.1 is not claimed to be exhaustive but is intended to provide examples of the legal points of reference for health economic evaluations and thresholds in Austria.

Handsuche von entscheidungsrelevanten Dokumenten im Kontext „Wirtschaftlichkeit"

- In the second step (Chapter 5.2), we summarised the current situation regarding the use of health economic evaluation in the decision-making process in Austria. For this task, we relied on relevant publications and context-specific knowledge.

Status quo von HEE in AT

- In the final step (Chapter 5.3), we present the options for implementing a threshold value in the reimbursement process in Austria. We contrasted the findings from RQ1-3 with the Austrian system context information (identifying pros and cons and implementation requirements).

Übersicht Empfehlungen & Optionen hinsichtlich Anwendung von HEE in AT

2.6 Quality Assurance of the Report

As part of quality assurance, the report was reviewed by an internal reviewer (CW) and two external reviewers (JO, MSK). The external reviewers were primarily asked to assess the following quality criteria:

Qualitätssicherung des Berichts durch interne & externe Reviewer*innen

- **Technical correctness:** Is the report technically correct (evidence and information used)?
- Does the report **consider the latest findings** in the research area?
- **Adequacy and transparency of method:** Is the method chosen adequate for addressing the research question, and are the methods applied transparently?
- **Logical structure and consistency of the report:** Is the report's structure consistent and comprehensible?
- **Formal features:** Does the report fulfil formal criteria of scientific writing (e.g. correct citations)?

The AIHTA considers external peer review by scientific experts from different disciplines to be a quality assurance method of scientific work. The responsibility for the report content lies with the AIHTA.

3 Health Economic Evaluation Methods and Thresholds

3.1 Introduction to Health Economic Thinking

3.1.1 Health Economics and Health Economic Data

HEE liefert Infos für Entscheidungsträger & die Politik über effizienten Ressourceneinsatz

The primary purpose of health economic evaluations (HEE) is to make a statement about the efficient use of resources to inform decision and policy makers in the health care system [3, 4]. The terms decision and policy maker are sometimes used interchangeably in the literature. Competencies of policy- and decision-making can overlap. However, in practice, both entities have different competencies. In the threshold context, the term decision maker is mainly used for all individuals or legal entities responsible for a final decision and includes decisions on reimbursement or price negotiations. Policy-making is distinct from making the final decision. Policy makers usually set the political and economic conditions (institutional conditions) as far as possible [11].

Entscheidungsträger & Politik unterschiedliche aber auch Überschneidungen bei Kompetenzen

Bsp. für unterschiedliche Kompetenzen: Finanzierung & Erstattungsentscheidung von Medikamenten

An example of the division of these competencies is drug reimbursement decisions, including price negotiations. The policy maker sets the budget or decision-relevant efficiency threshold, and the decision maker conducts the reimbursement decision, including price negotiations and consultation of clinical and health economic evidence. In such a situation, the decision maker needs evidence of HEE to make reimbursement decisions.

Def. von HEE: Vergleich von mindestens zwei „konkurrierenden" Handlungsoptionen im Hinblick auf ihre Kosten & Folgen (Outcomes)

The terms HEE or health economic analysis apply only to studies in which at least two "competing" courses of action are evaluated comparatively in terms of their costs and consequences (outcomes) [3]. Evaluations that only compare either the consequences or costs of two competitive interventions are only partial evaluations. The same principle applies to evaluations that do not compare at least two alternatives. Table 3-1 provides an overview of the distinction between partial HEEs and full HEEs.

Table 3-1: Distinction between partial evaluations and full health economic evaluations (Table based on Drummond et al. [2015], own depiction)

Comparison	Examines only consequences (outcomes)	Examines only costs (inputs)	Examines costs (inputs) and consequences (outcomes)
No comparison of competing interventions	■ Outcome description	■ Cost description	■ Cost-outcome description
Comparison of (at least) two competing interventions	■ Efficacy or effectiveness evaluation	■ Cost analysis, e.g. cost-minimisation analysis	■ Cost-effectiveness analysis including cost-consequence analysis ■ Cost-utility analysis ■ Cost-benefit analysis

Partial evaluation
Full health economic evaluation

verschiedene Vergleichsebenen:

neue Intervention vs. „Goldstandard"

"Competing" means that patients can only receive one of the interventions or one specific combination of different interventions (mutually exclusive). Different intervention combinations can also be different orders of sequences in a screening or diagnostic process. The comparison in full HEE is usually between the (new) intervention of interest and the "gold standard" or standard of care[6] (SOC) in the same disease class or for the same indication.

Vergleich über Indikationen, Populationen & Sektoren hinweg

However, comparisons are also carried out across indications, populations, disease classes, or sectors [3, 10, 29]. Competition in the economic sense means that different interventions or policies for different populations compete with each other. Whether these cross-sector comparisons are ethically legitimate is not addressed in standard HEE. Within an HTA report, such ethical questions may be addressed separately [10].

verschiedene Formen der HEE: „Huckepack"-Analyse vs. entscheidungs-analytisches Modell

Health economic data can be collected and analysed alongside a clinical trial (piggyback evaluation) or standalone modelled using decision analysis (DA). The latter approach uses mathematical techniques such as Markov models and is based on parameter assumptions of the relevant population, diseases, and intervention of interest. Modelling studies utilise data from other (clinical) studies, such as mortality rates or health state transition probabilities, for the model input parameters. Each approach has its advantages and disadvantages [30].

zentrale Konzepte im ges.ök. Denken: Opportunitätskosten, Effizienz, Utilitarismus & (Extra-)Welfarismus

Various central concepts in economic thinking are essential to understanding health economics and HEE:

- Economic Costs and Opportunity Cost Approach.
- Efficiency, Utilitarianism, Welfarism, and Extra-Welfarism.

3.1.2 Economic Costs and Opportunity Cost Approach

Definition of Economic Costs and Opportunity Cost

Unterscheidung: ökonomische bzw. Ressourcen- vs. monetäre Kosten

Geld nicht das zentrale Problem → Gesundheitsökonomie beschäftigt sich mit temporärer Ressourcenknappheit

Economic costs, i.e., the use of labour and resources for specific purposes, should not be confused with monetary costs or expenditures (i.e., the use of money). As stated by Mushkin [1958, p. 792] referenced by Turner et al. [2023]:

> *"The health administrator has usually equated 'health economics' with 'money questions in the field of health'. But, money is not the central problem of health economics. Health economics is concerned with the optimum use of* ***[temporarily; note from the authors]*** *scarce economic resources for the care of the sick and the promotion of health, taking into account competing uses of these resources."* – Mushkin [1958, p. 792]

This quote provides an adequate definition of health economics that reflects the distinction between economic resources and financial means (money) Turner et al. [2023].

[6] The gold standard is not the ultimately perfect intervention, but the best available intervention in the same disease class: *"Studies that evaluate a new diagnostic test, procedure, or method should do so by comparing it with a time honoured alternative that is considered to be the current standard in the field. […] "Gold standard" is the popular term to describe this […] Gold standard is a historical term borrowed from economists. It signifies a monetary standard, under which the basic unit of currency was defined by a stated quantity of gold."* – Claassen [2005, p. 1121]

zentrales Konzept im polit-ökonomischen Denken: Opportunitätskosten (Opp.-Kosten)

One of the central concepts of economic thinking to arrive at economic costs is the opportunity cost approach. Suppose decision-makers in the healthcare system hire nurses, physicians, and other personnel or use other resources for a particular need. In that case, they are no longer available to the rest of the economy. This loss of production potential or "opportunities" elsewhere is referred to in economics as "opportunity cost". Opportunity cost is the "price" of real resources that a decision or policy maker pays to keep the healthcare system running instead of using the resources for alternative purposes. Hence, opportunity cost is not a monetary but a "real" cost.

Opp.-Kosten = „Preis" des realen Ressourceneinsatzes

ökonomische Kosten = Opp.-Kosten plus buchhalterische Kosten

The mathematical identity for economic costs can be derived from the following definition. Economic costs include opportunity cost plus (financial) accounting costs:

$$Economic\ costs = Opportunity\ cost + Accounting\ costs$$

Bsp. buchhalterische Kosten: Abschreibung von Kapital

Financial or accounting costs capture the depreciation of capital resources and are used for budgeting and financial planning purposes. Opportunity cost captures the need to make decisions about temporarily and spatially scarce resources (see Table 3-2). Economic decision-making, in turn, reflects the competing relationship between different interventions and the competing nature of using different input resources [32].

Def. von Opp.-Kosten:

Turner et al. [2023] offer the following definition of opportunity cost:

„Wert" der nächstbesten Alternative, auf die verzichtet wird

> *"By pursuing one action, the potential benefit that could have been gained from the* ***next-best alternative*** *action is sacrificed – which is known as opportunity costs. […] or […] more formally, the opportunity cost of making a particular choice is the value of the next-best alternative that is foregone"* – Turner et al. [2023, p. 2]

… ,or in short, opportunity cost is the …

> *"benefits forgone by particular use of resources"* – Palmer and Raftery [1999, p. 1551]

Darstellung Opp.-Kosten:

Economic and opportunity cost should be expressed in natural units or health-related quality of life (HRQoL) measures, such as healthy life years lost. Culyer [2015] also emphasises that …

natürliche Einheiten wie gesundheitsbezogene Lebensqualität

> *"[…] the true opportunity cost of health care in a community, where the effectiveness of interventions is determined by their impact on health, is not to be measured in money – but in health itself."* – Culyer [2015, p. 13]

Umrechnung in monetäre Einheiten aufgrund Vergleichbarkeit

Economic costs are transferred in monetary currencies only for comparability reasons.

Identification, Measurement, and Valuation of Economic Costs

dreistufige Ermittlung ökonomischer Kosten:

Turner et al. [2023] describe the process of estimating economic and financial costs in three steps:

1. **Identification:** determining the resources needed to implement the interventions of interest and associated tasks from the relevant perspective, such as the payer perspective, health care provider perspective, healthcare system perspective, or societal perspective. **Identifikation**
2. **Measurement:** measuring the amount of the needed resources to provide the interventions. **Messung/Quantifizierung**
3. **Valuation:** Valuing each necessary resource by placing a monetary (or non-monetary) amount on it ("price labelling"). **Bewertung („Price Labelling")**

Zusammenhang Opp.-Kosten & Ressourcenbewertung im 3. Schritt hergestellt

The decisive point in this "Identification, Measurement, and Valuation" (IMV) approach to distinguish between the economic and account cost is the third one – Valuation. The opportunity cost approach is used in the third step when calculating economic costs. Economic costs comprise all relevant resources an intervention consumes, not just the costs affecting the available financial budget or expenditures. Economic cost also values resources and components of interventions for which no market prices are available, or no price has been paid. For example, economic costs consider depreciation costs of capital (financial/accounting item) and the opportunity cost associated with using resources bound by capital, e.g. foregone interest payments received[7].

Table 3-2 gives an overview of the differences between economic and financial costs based on the depiction by Turner et al. [2023].

Table 3-2: Difference in economic cost and financial costs based on Turner et al. [2023]

	Economic cost	Financial/Accounting cost
Description	Economic costs represent the total value of resources needed to implement the relevant intervention. Economic costs include opportunity cost, i.e., the value of the foregone next-best alternative. Economic costs are relevant in analyses, which assess the efficiency of "competing" courses of action such as health care interventions or general policies. The research question, context, perspective, and time frame impact economic costs. Especially, the study perspective (individual, healthcare system, etc) has substantial impacts on which costs and effects are included in the evaluation.	From an accounting perspective, financial costs represent the actual money or expenditures spent on resources, goods, and services. Financial costs capture the depreciation of capital resources and are used for budgeting and financial planning purposes. For example, the Ministry of Health or Social Security institutions use financial costs to plan the healthcare system. These costs are also relevant in budget impact analyses (BIA). A BIA is an economic assessment that estimates the financial consequences of adopting a new intervention and can be performed in addition to HEE.
Costs included	All resources/resource costs relevant from the perspective taken.	Goods, services, inputs purchased and the time-dependent depreciated value of capital.
Valuation	Market prices are used as a proxy. In the absence of market prices, a "shadow price" is estimated. A shadow price is an estimated price that reflects the valuation of the good, service or intervention (see Table 3-6 for an overview of the estimation approaches of shadow prices).	Market prices/actual paid prices

Opportunity Cost and the Perspective

Bewertungsperspektiven haben Auswirkungen auf Opp.-Kosten & Kosten-Nutzen-Analysen

Perspektiven: Patient*innen (Pat.), Sozialversicherung, Gesundheitssystem & gesellschaftliche Sicht

In health policy and decision-making, a crucial aspect in determining opportunity costs is the perspective. The perspective is the adopted viewpoint that defines which types of costs and outcomes to consider and determines who bears the costs [35]. Different perspectives include those of the patient, healthcare payer, healthcare providers, healthcare system, and society [35, 36]. Costs and benefits can vary significantly depending on the perspective taken [37, 38]. Therefore, before conducting a HEE, the perspective must be determined as it has implications for relevant costs, benefits, and study design, with the societal perspective being the broadest and reflecting the full range of costs and benefits [35, 36, 39]. The health economic literature makes a further distinction regarding where or on whom opportunity costs fall, depending on the approach used. However, we show that this distinction is merely ostensible (see next Section 3.1.3 on Welfarism versus Extra-Welfarism).

[7] Opportunity costs included in economic costs are often also time costs. Therefore, to account for these time (opportunity) costs, costs are annualised and standardised by an annualization factor: *Annualisation factor = depreciation rate + opportunity cost associated with the bounded capital (e.g., interest rate)*

Objektive Messung von Opp.-Kosten & Effizienz kann Verteilungsungleichheiten & …

Opportunity cost and (technical) efficiency are universal economic concepts that should be measured objectively, particularly from a societal perspective, independent of subject and sector. While a scientifically objective measurement approach acknowledges that opportunity costs may be distributed unequally among different economic agents, with some benefiting more or bearing greater costs than others, it does not prevent these distributions from being judged as unfair. In fact, an objective measurement may reveal that the resulting distribution of benefits and costs is highly inequitable.

… zugrundeliegende Machtstrukturen aufzeigen

The assessment of opportunity cost is not only dependent on the perspective taken, but each analysis itself reveals insights about the perspective taken. As with inequalities in income or other economic variables such as inflation or capital, the distribution of opportunity costs and benefits is influenced by those who hold authority over their allocation – a reflection of power distribution and its dynamics.

Opp.-Kosten-Analyse ermöglicht

Therefore, analysing opportunity costs in decision-making can reveal the underlying power dynamics that may cause a perceived inequitable distribution of costs and benefits, by:

- Exposing power structures and dynamics:
  - Demonstrates who can influence the decision process
  - Shows whose values are prioritised
  - Reveals who has authority over resource allocation
- Making distributions transparent:
  - Shows who bears costs vs. who receives benefits
  - Reveals whose alternatives are considered or ignored
  - Highlights differential impacts across economic agents
- Making allocations traceable:
  - Documents which costs/benefits are included/excluded
  - Shows how burdens are distributed across groups
  - Reveals whose interests shape the decision framework
- Enabling accountability:
  - Creates record of distributional impacts
  - Makes power dynamics explicit rather than implicit
  - Allows tracking of who gains and loses

Darstellung von Machtstrukturen & -dynamiken

Transparenz

Nachvollziehbarkeit der Allokationen

Rechenschaftspflicht („Accountability")

Transparente Dokumentation der HEE & deren Bedeutung für gerechte Entscheidungen

Transparency and traceability can then inform more equitable decision-making processes and highlight where power imbalances affect outcomes. Therefore, HEE should explicitly specify their adopted perspective. Any omitted items must be explicitly acknowledged, with clear explanations for their exclusion and a discussion of how these omissions might affect the final results [39].

Opp.-Kosten-Denken in Entscheidungsprozessen nicht zwingend ein Nullsummenspiel

However, objective measurement and an unequal distribution do not mean that opportunity cost thinking in decision-making situations is unavoidably a zero-sum game. A zero-sum game is a situation where one participant's gain is exactly equal to another participant's loss: what one economic agent wins, another must lose, with the sum of all gains and losses equalling zero. Although zero-sum games exist in political economy, decision-making about resource use, and consequently considerations of opportunity cost, are generally not zero-sum games. If they were exclusively zero-sum games, economic growth, national accounting and the creation of surplus value would simply not be possible.

3.1.3 Efficiency, Utilitarianism, Welfarism, and Extra-Welfarism

Efficiency and Utilitarianism

Effizienzbegriff in Gesundheitsökonomie: bestmögliche Ressourcennutzung & Minimierung von Opp.-Kosten

The explicit presentation of economic costs is a prerequisite for the primary purposes of HEEs: to make a statement on the efficient use of resources and to inform decision and policy makers in the healthcare system. Several concepts and definitions of efficiency exist in economics. A common definition of efficiency in health economics is that efficiency measures whether healthcare resources are used to get the "best value for money" when comparing a new intervention with an existing one [40]. Another definition states that efficiency is achieved when the opportunity cost of an intervention are minimised and benefits are maximised [41].

verschiedene Effizienzkonzepte & deren Anwendbarkeit in der Gesundheitsökonomie

However, the first definition, "best value for money", is vague, and each efficiency concept is also based on specific theoretical assumptions. For example, economic efficiency in health economics relates to the orthodox concept of market or allocative efficiency, which is disputable. The same applies to Pareto efficiency (see Table 3-4). In any case, efficiency in health economics addresses the relation between available resource inputs (labour force, capital), and intermediate outputs (numbers of treated patients, inpatient days, waiting times, etc.) or outcomes (e.g., decreased mortality, improved clinical outcomes such as blood pressure or cholesterol) and final health outcomes (e.g., life years gained)[8] [40].

3 Konzepte:

Three concepts of efficiency are often used in the health economic literature [40]:

- Technical efficiency addresses the issue of using given resources to maximise the output. **technische Effizienz**
- Productive efficiency refers to the selection of different resource combinations in order to maximise the health benefit at a given cost. **Produktionseffizienz**
- Allocative efficiency means finding the right mix of health programmes to maximise the health of society. **allokative Effizienz**

Effizienzkonzepte: Beziehung zwischen technischer, produktiver & allokativer Effizienz

According to Palmer and Torgerson [1999], productive efficiency implies technical efficiency, and allocative efficiency implies productive efficiency. However, that does not hold the other way around. Given limited resources, the concept of productive efficiency will exclude some technically efficient combinations of resource inputs as "inefficient", and the concept of allocative efficiency will eliminate some productively efficient resource allocations [40].

neoklassische Effizienzkonzepte, wie Pareto-Effizienz, scheitern an polit-ökonomischer Realität

However, these definitions leave room for interpretation, and it seems that researchers have different views of "efficiency". This "problem" arises from the fact that health economics is based on neoclassical economic theory. For example, the allocative and Pareto efficiency concepts do not hold in reality because they rest on strict assumptions derived from neoclassical economic theory, such as perfect competition. Perfect competition does not apply to real markets and is especially violated in the provision of health commodities and services. Pareto efficiency is also hardly met from a political economy perspective. For example, providing health care for the population through government agencies would reduce private sector profits.

[8] This efficiency definition refers to the concept of technical or process efficiency, which is inherent in any decision related to production. Furthermore, technical efficiency is related to an engineering notion of efficiency, examining the use of inputs (power per unit) of some output [42].

Tabelle 3-4 beschreibt Effizienzkonzepte

Table 3-4 shows the most often used concepts of efficiency, their definitions, and further details regarding the implications for health economic thinking.

Effizienzdenken in der Gesundheitsökonomie eng verbunden mit Utilitarismus-Prinzip der Nutzenmaximierung

Efficiency considerations and health economic thinking are closely linked to the philosophical school of utilitarianism. Utilitarianism is a form of consequentialism. An action from a utilitarian point of view is "right" if it maximises the aggregated sum of the well-being of all affected individuals [43]. Hence, the consequences of any action are the only standard of right and wrong. This contrasts with deontological ethics, which states that an action is morally right if it follows prespecified rules and principles.

mögliche Trade-offs zwischen Effizienz & (Verteilungs)Gerechtigkeit im Gesundheitswesen

A key assumption of utilitarianism is that maximising the "greatest happiness", e.g., healthy life years or positive monetary net benefits, is in the interest of several actors: the state, private companies or the "economy", and in the interest of the affected individuals. However, the utilitarian principle applied in health care by establishing efficiency can lead to discrimination of specific population groups. There can be trade-offs between efficiency and equity [44]. Yet, Marseille and Kahn [2019] argue that the conflict between equity and efficiency may be smaller than expected. People affected by material deprivation usually have a higher risk of illness and may make use of health services more often. People affected by poverty are then those for whom the utility is maximised because they gain the most from provided health care services. Thus efficiency and equity goals may be aligned in most cases [45].

Evidenz zu Zusammenhang sozioökonomischer Ungleichheit & erhöhten Opp.-Kosten

However, whether this applies to a real healthcare setting is questionable, as people affected by poverty may seek less health care for non-emergency cases because of factors such as stigmatisation or limited access [46, 47]. Evidence from the UK shows that the opportunity cost of government expenditure on health is higher for lower socioeconomic groups. Love-Koh et al (2022) published a paper with the socioeconomic distribution of health effects from health care expenditure changes for the English population [48]. Undertaking distributional cost-effectiveness analysis informed by this kind of data is an alternative to equity weighting analyses.

Brouwer & Koopmanschap (2000): Equity-Gewichtung widerspricht utilitaristischem Prinzip der individuellen Nutzensummierung …

Brouwer and Koopmanschap [2000], in turn, argue against the use of equity weights, because this would contradict the application of "classical utilitarianism". They state that

> *"Equity weights may imply that individual utility may be 'corrected' or weighted from a societal level. Classical utilitarianism which sets social welfare equal to the sum of individual utilities is abandoned therefore."* – Brouwer and Koopmanschap [2000, p. 443].

… aber klassischer Utilitarismus nach Bentham schließt auch Verteilungsaspekte mit ein

However, this assertion on "classical utilitarianism" and the interpretation are questionable. The original idea of Bentham's utilitarianism was that the maximum level of happiness for society as a whole should also consider the specific way in which goods and rights are distributed – hence also equity aspects:

> *"So far as depends upon wealth, – of two persons having unequal fortunes, he who has most wealth must by a legislator be regarded as having most happiness. But the quantity of happiness will not go on increasing in anything near the same proportion as the quantity of wealth: – ten thousand times the quantity of wealth will not bring with it ten thousand times the quantity of happiness. It will even be matter of doubt, whether ten thousand times the wealth will in general bring with it twice the happiness. Thus it is, that, the effect of wealth in the production of happiness goes on diminishing, as the quantity by which the wealth of one man exceeds that of another goes on increasing: in other words,*

> *the quantity of happiness produced by a particle of wealth (each particle being of the same magnitude) will be less and less at every particle; the second will produce less than the first, the third than the second, and so on."* – Bentham [2011, p. 275]

QALY-Maximierung in CUA vernachlässigt (meist) sozioökonomische Faktoren

This quote demonstrates that the original classical utilitarianism took distributional aspects into account. This includes the consideration of the underlying income distribution and the distribution of health risks of population. Additionally, one can find the concept of diminishing marginal utility in this quote. This may be different from the utilitarianism concept in a classical cost-utility analysis as used within HEE (see Chapter 3.2.2 on Cost-Utility Analysis (CUA)): quality-adjusted life years (QALYs) are maximised, while the social aspect, wealth, or the initial endowment do not play a role. An additional QALY for a person with a low income is worth the same as a QALY for a person with a higher income, even though these two groups have different life expectancies.

teils widersprüchliche Rechtfertigung des Utilitarismus durch deontologische Prinzipien in der Literatur

Some authors, e.g., Marseille and Kahn [2019] concluded that despite its limitations, utilitarianism is still superior to alternative ethical principles, because maximising health benefits under a budget constraint is itself an important ethical value. This statement suffers from a circular argument. Whether a specific action is morally right or wrong can be only "confirmed" ex post – after the utilitarian calculation applied to a specific action. As mentioned, utilitarianism is a consequential approach and in contrast to deontological philosophical concepts, which adhere to ex ante criteria. Therefore, the general judgment that the utilitarian principle has a value itself is a statement applying deontological principles.

„moderner" Utilitarismus:

Nevertheless, the application of utilitarianism has advantages over other ethical concepts. Ritschel [2018] cites from Kramer-McInnis [2008] book on Bentham[9]:

"Verbindung von materialistisch-wissenschaftlichem Denken, Individualismus & gesellschaftlichem Wohlergehen

> *What characterizes modern utilitarianism according to individual pursuit of pleasure and social welfare […] is its close connection with materialism and the mathematical-experimental scientific model of the Enlightenment era. We can therefore generally characterize modern utilitarianism with the attributes materialistic, individualistic and social-eudemonistic (not just individual happiness)."* – Kramer-McInnis [2008, p. lix-lx]

Transparenz & Nachvollziehbarkeit utilitaristischer Berechnungen ermöglicht kritische Begutachtung

In addition, utilitarianism can function as a corrective to arbitrariness. A transparent utilitarian calculation is comprehensible and can be criticised, regardless of whether it comes from the pharmaceutical industry, public bodies, the state, or other stakeholders. This was already outlined in Section 3.1.2 on Opportunity Cost and the Perspective.

Welfarism versus Extra-Welfarism

Welfarismus & Extra-Welfarismus: unterschiedliche Ansätze zur Bestimmung von Opp.-Kosten, aber theoretische Abgrenzung nicht immer eindeutig

In the literature, some health economists make a distinction between a welfarist and an extra-welfarist approach to determine opportunity cost including benefits. There seems no clear-cut consensus on the definition of welfarism in the literature. According to Brouwer et al. [2008], some scholars, like Culyer [2012], restrict welfarism to specific characteristics like utility from health. Others adopt the approach by Bergson [1938], allowing unlimited factors to be included in a social welfare function, such as processes, equity, in-

[9] The original quote is in German and was translated by the authors of the report.

terpersonal relationships, institutions, social norms, and beyond, provided these elements can be measured through individual utility [53]. While welfarism seems "relatively" better defined due to its roots in Neoclassical theory (welfarist economics) and longer theoretical tradition, extra-welfarism contains more significant conceptual ambiguities. [49, 53].

Extra-Welfarismus als Erweiterung des Welfarismus

Extra-welfarism represents an attempt to move beyond traditional welfare economics, but its exact departure points and new directions remain debated [53]. For extra-welfarism to be meaningful, it must provide something distinct from welfarism, despite welfarism's allegedly more comprehensive scope. Therefore, no clear consensus definition of extra-welfarism emerged until today [53]. The main differences according to the literature are the following [49, 53, 56]:

Table 3-3: Differences between the welfarist and extra-welfarist approach based on information in Brouwer and Koopmanschap [2000], Brouwer et al. [2008], Claxton et al. [2010]

Difference	Welfarist	Extra-Welfarist
Theoretical foundation	Neoclassical economic theory (Welfare economics): ■ Rational utility maximisation ■ Individuals best judge their utility ■ Utility comes from outcomes not processes ■ Social welfare based on individual preferences	"Broader" social objectives: ■ Allows for multiple measures of wellbeing beyond individual preferences ■ Supports the "decision making" that considers objectives and constraints of decision makers ■ Recognises budget constraints as legitimate expressions of social values
Scope/Focus (Benefits/Outcomes)	Utility maximisation	Health (outcomes) maximisation including quality adjustments
Type of HEE (evaluation method)	Uses Cost-Benefit Analysis as primary evaluation tool	Uses Cost-Effectiveness/Cost-Utility Analysis as primary evaluation tools
Valuation	Values outcomes based on individual willingness to pay (WTP) and/or market prices	Uses Health-specific measures (QALYs etc.)
Sources of valuation	Individual	Social/Expert judgement
Perspective (in practice)	Typically uses societal perspective	Typically uses healthcare system perspective
Opportunity cost	Opportunity cost (utility gains) falls on society	Opportunity cost (health gains) falls on healthcare system
Further characteristics	■ Based on individual utility/preferences ■ Considers all sources of utility ■ Rooted in neoclassical welfare economics ■ Considers all foregone alternatives ■ Matches broader welfare economics	■ Goes beyond individual utility ■ Focuses specifically on health outcomes ■ Allows consideration of non-utility information ■ Displaces other healthcare interventions ■ Matches real-world budget constraints

Claxton et al (2010): Vereinbarkeit von Extra-Welfarismus & Welfarismus nur unter restriktiven Bedingungen

Claxton et al. [2010] argue that several studies have explored how extra-welfarist approaches in the form of CEA or CUA fit within welfare economics, but they claim that strong assumptions are needed for CEA or CUA and CBA to reach similar conclusions specifically for the healthcare context. For example, for CEA to align with welfarist principles, it must account for all costs, including future medical spending (both related and unrelated), consumption, and productivity impacts [56, 57]. For CUA to align with maximising societal welfare, the marginal utility of income used to fund healthcare must be equal across all healthcare interventions [58]. Claxton et al. [2010] state there is also an ongoing debate about whether CEA or CUA should fully consider societal costs in the analysis at all [56].

Dominanz des Extra-Welfarismus in der Gesundheitsökonomie, aufgrund besserer Eignung für gesundheitspolitische Entscheidungen

Welfare economics has been also criticised as unsuitable for personal ethics, being seen as calculating, uncaring, and focused solely on outcomes. However, it is also considered appropriate for public policy-making. While a societal approach in the sense of a welfare economic approach may be theoretically justified, its practical implementation presents challenges, particularly when individual interests conflict with societal objectives [39, 59]. Therefore, the extra-welfarist approach with its characteristics, as defined in Table 3-3, has become dominant largely because some health economists argue that it better aligns with healthcare decision-making needs and social objectives [56].

Grenzen des Extra-Welfarismus: ungelöste Bewertungskonflikte, v. a. bei komplexen Interventionen

In contrast, Buchanan and Wordsworth [2015] argue that the extra-welfarist approach may not capture all aspects relevant to decision-making, especially when evaluating complex interventions. They found that one in five studies applying both welfarist and extra-welfarist approaches yields conflicting adoption recommendations, with no clear pattern of which approach provides better evidence. Moreover, only 10% of studies guide decision-makers on which results to prioritise. Buchanan and Wordsworth [2015] conclude that this creates uncertainty about value-for-money judgments, and health economists typically fail to provide adequate guidance to resolve these contradictions.

Birch & Donaldson (2003): Unterscheidung zwischen Welfarismus & Extra-Welfarismus weniger bedeutend als angenommen

In addition, Birch and Donaldson [2003] state that limitations commonly attributed to welfarism stem from its application rather than theoretical constraints, and that extra-welfarist justifications are fundamentally rooted in welfarist arguments. They also discovered that extra-welfarist practices like QALY measurement methods share theoretical foundations with welfarist approaches like WTP[10], with WTP methods handling measurement challenges more effectively. Based on these findings, the authors question the distinct contribution of extra-welfarism to health resource allocation decisions, suggesting that the separation between welfarist and extra-welfarist approaches may be less substantial than widely believed [61].

Gesundheit vs. Nutzen: Coast's (2009) Kritik an konzeptioneller Ähnlichkeit von Welfarismus & Extra-Welfarismus

Coast [2009] critiques the identify of welfarism and extra-welfarism. Coast [2009] claims that extra-welfarism, by shifting from utility (welfarism) to health (extra-welfarism) as its evaluative space, cannot separate efficiency and equity as welfarism does. Any maximisation in the health evaluative space implies the acceptance of an ethical basis of utilitarianism aligned with Bentham's felicific calculus. Coast [2009] maintains that only welfarism, grounded in Neoclassical economics, can maximise utility without incorporating ethical or deontological criteria. According to Coast [2009], utility in (normative) economics is *"a quantity that an individual should maximise or that society should help him to maximise"*. The economy produces commodities and consuming these commodities (including health-related commodities), services, or leisure generates (expected) utility. According to Coast's welfarist view, health outcomes from healthcare services are not valued directly, but only through their contribution to (expected) utility.

Implizite Werturteile auch Teil des Welfarismus

Coast [2009] argues that extra-welfarism treats health as intrinsically valuable, independent of its utility effects – a valuation established beforehand. In this framework, health exists as a physical stock that individuals possess and can be enhanced through resource allocation to health services. Coast's position represents a logical fallacy. The separation of efficiency and certain moral aspects is unattainable in welfarism as well. Her welfarist approach pre-

[10] See Chapter 3.4.3 on Universal ICER Thresholds and Societal Willingness to Pay ICER Thresholds (Societal WTP Thresholds) for an explanation on methods to elicit the WTP.

supposes that the distribution of production means for producing utility-generating commodities is equitable, an assumption embedded in the analysis from the start, thus making an implicit value judgment.

Extra-Welfarismus als gesundheitsspezifische Projektion des allgemeinen Welfarismus-Konzepts

In the light of these contradictions and disputes, we argue that welfarism and extra-welfarism are conceptually similar, share common characteristics but are also analytically distinct. On the one hand, both are utilitarian concepts, because they rest upon utility maximisation:

- **Welfarism:** Maximisation of general utility ("Welfare")
- **Extra-welfarism:** Maximisation of health-specific utility (projected into health space)

The extra-welfarist approach can be seen as a projection (or specific case) of the broader welfarist approach. Extra-welfarist measures (like QALYs) are essentially a subset of broader utility or special case of the more general welfarist framework but restrict the utility space to health-related dimensions.

Unterschiede zwischen Welfarismus & Extra-Welfarismus durch praktische Anwendung bedingt

On the other hand, we also agree with health economists who argue that both analytical approaches are distinct [39, 56]. But our argument may be potentially different from others. The differences between welfarism and extra-welfarism emerge primarily from practical application, driven by real world constraints such as measurement challenges and politically determined budgets, rather than theoretical foundations.

Vorteil des Extra-Welfarismus: Fokus auf Gesundheitsmaximierung & praktische Umsetzbarkeit

Therefore, some health economists advocate for the extra-welfarist approach precisely because its deliberate focus on health maximisation and restriction to the healthcare domain makes it more practical to implement and evaluate within existing healthcare systems. As mentioned in the Section on Efficiency and Utilitarianism, market values (prices) are distorted because markets do not behave as Neoclassical economic theory suggests or prices to valuate costs and benefits may be even not available [63]. Therefore, extra-welfarist analyses (CEA or CUA) typically align with a healthcare system perspective and opportunity costs falling on healthcare budgets.

Extra-Welfarismus entspricht eher Benthams Utilitarismus

Besides the similarities and differences of both approaches, we would even argue that an extra-welfarist approach is more in line with the original idea of Bentham's utilitarianism, which also takes into account equity aspects (see Efficiency and Utilitarianism).

Zusammenfassend: Unterscheidung von Welfarismus & Extra-Welfarismus, eher in praktischer Anwendung zu suchen

In summary, the perceived distinction between welfarism and extra-welfarism are practical/operational, not theoretical in an epistemological sense. This insight helps explain why debates about their theoretical differences sometimes miss the point – extra-welfarism and welfarism are not fundamentally different approaches, but rather different practical implementations of the same underlying utilitarian concept.

Table 3-4: Efficiency concepts and definitions

Efficiency concept	Definition	Examples, implications and use within health economics
Technical efficiency	Technical efficiency pertains to the physical relation between input resources (labour force, capital), and intermediate outputs (numbers of treated patients, inpatient days, waiting times, etc) or final health outcomes. A combination of a given limited set of input resources is technically efficient if the maximum possible outcome is achieved, or a specified outcome is technically efficient if this outcome can be achieved with the lowest combination of inputs. A health care intervention is technically inefficient if the same (or greater) outcome could be obtained with less than one type of input [40].	Dose-response relationship: Dose-response analysis is useful not only for analysing the potential harms of high medicinal doses but can also give indications of whether a lower dose of a drug is more efficient than a higher dose. For example, higher than standard daily doses of selective serotonin reuptake inhibitors (SSR) are associated with higher dropout rates and a greater incidence of adverse drug effects. Standard doses of SSRIs are optimal, hence technically efficient . Another example is the treatment of osteoporosis using alendronate: a 10 mg daily dose is as effective as a 20 mg dose. In both cases, the lower dose is technically efficient [40, 64]. Health system efficiency (efficiency variations of decision-making units, DMUs): Technical efficiency or productivity can be examined via data envelopment analysis (DEA) or stochastic frontier analysis (SFA). With these two approaches, the efficiency of a health system, like the efficiency variations of hospitals, can be analysed, and it can be inferred whether health inputs are efficiently used or whether there is potential room for improvement. This is done by setting health outcomes (infant survival rates, maternal survival rates, healthy life years) and health inputs (health expenditure, medical personnel, hospital beds etc.) into a relation [65].
Productive efficiency	Productive efficiency is a relative concept and an extension of technical efficiency. Productive efficiency regards choosing different combinations of resource inputs to achieve the maximum health benefit given the relative costs of the resource inputs. Production efficiency is achieved if one can no longer produce additional amounts of output (commodity, service, health outcome) without lowering the "production level" of another output. The difference to technical efficiency is that within productive efficiency, cost minimisation is achieved by adjusting the mix of inputs (mathematically: average total costs = marginal costs). Technical efficiency is output maximisation from a given mix of inputs. Productive efficiency enables the evaluation of the relative value for money of interventions with directly comparable outcomes [40].	Comparisons of different interventions for different diseases: For example, Palmer and Torgerson [1999] mention the example of a health policy change in the context of Down's syndrome. Although a change from maternal age screening to biochemical screening requires fewer amniocenteses, biochemical screening requires another resource – biochemical testing. The choice of interventions depends on the relative costs of these different inputs. Suppose the cost sum of the biochemical screening programme is smaller than or the same as the maternal age programme, and outcomes are equal or better. In that case, the biochemical programme is more efficient than the maternal age screening [40].
Allocative or market efficiency (competitive equilibrium)	Allocative or market efficiency is a theoretical outcome within the assumptions of neoclassical economics. For allocative efficiency to be established, the assumption of perfect competition or perfect markets needs to be satisfied. In an allocative equilibrium (efficient allocation), prices and quantities of commodities or services are optimal. In a competitive equilibrium, marginal costs equal marginal benefits, meaning that the value society places on a commodity or service (output) equals the value of the resources given up (inputs) [66, 67].	Empirically, the concepts of perfect competition and allocative efficiency do not apply to markets observed in reality. Neither markets in general nor markets for health commodities and services are markets with perfect competition [67]. Perfect competition states that small profit-maximising and price-taking firms do not impact the market. Further assumptions are that there are no government interventions, no barriers to entry or exit, equal access to factors of production by firms, and no information asymmetries leading to supply-induced demand [67]. In a perfectly competitive equilibrium with allocative efficiency, the value society places on a commodity (the price or marginal benefit) is equivalent to the value of the resources given up to produce it (the marginal costs) [66]. The myth of perfect competition can be easily observed in markets for health commodities, where a few providers provide services (public hospitals), patented medicines or medical devices (private companies) for specific indications. This resembles instead a monopolistic market, where the price is greater than the marginal costs. A monopoly will not produce at this point, and it will produce too little output at a cost that is too high.
Pareto efficiency	Pareto efficiency is related to allocative/market efficiency: An allocation (economic outcome) is Pareto efficient or optimal if *"it is impossible to make some individuals better off without making some other individuals worse off. This concept is a formalization of the idea that there is no waste in society, and it conveniently separates the issue of economic efficiency from more controversial (and political) questions regarding the ideal distribution of well-being across individuals."* – Mas-Colell et al. [1995, p. 307]. The normative intuition of the Pareto concept is simple: If a group of people (or an individual) prefers a certain outcome and it does not cost anyone else, society should give that group of people (or individuals) what they want [68].	Pareto efficiency is also hardly met in reality from a political economy perspective. A policy favouring one group over another is a daily political practice. For example, providing health care through government agencies would reduce existing private sector profits [69].

3.2 Types of Health Economic Evaluations

3 Formen von HEE: Kosten-Effektivitätsanalyse (CEA), Kosten-Nutzwert-Analyse (CUA) & Kosten-Nutzen-Analyse (CBA)

Health economists distinguish between three main types of evaluation methods: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA) [3] (see Table 3-1). Cost-minimisation analysis (CMA) or pure cost studies are no longer considered genuine health economic evaluations. These studies are only an appropriate analysis method in rare circumstances and are only recommended if certain conditions are met [70].

Hauptunterschied: Darstellung bzw. Einheit des analysierten Nutzens

The forms of evaluations differ according to the representation of the analysed benefits. While the costs are always mapped in monetary units, the benefits can be represented in natural units, generic utility values, or monetary units. The natural unit depends on the underlying disease or clinical picture, including blood pressure, cholesterol level, life years (LY) saved or lost, or mortality.

3.2.1 Cost-Effectiveness Analysis (CEA)

Kosten-Effektivitätsanalyse: Endpunkte in "natürlichen" Einheiten:

In this type of study, a clinical endpoint in a natural unit is compared with the costs [3]. Endpoints in natural units can be differentiated between …

- **Disease-specific clinical endpoints:** blood pressure, cholesterol level, cardiovascular events, pain, blood glucose levels, severity of depression, severity of psoriasis.
- **Generic endpoints:** progression-free survival (PFS), morbidity, life years saved or lost or mortality.

krankheitsspezifisch (z. B. Blutdruck, Schweregrad der Depression etc.)

generisch (Morbidität, Mortalität etc.)

CEA meist in Ländern ohne QALYs

According to the literature, CEA is of most use in jurisdictions where utility measures, e.g., based on health-related quality of life (HRQoL) measures, are not available or recommended as the benefit measure [3]. CEA is recommended in situations where a decision or policy maker wants to achieve a very specific health objective or if decision makers with a politically limited budget are considering only a limited range of interventions within a disease class [3].

Beispiel für CEA: West of Scotland Coronary Prevention Study (1995)

An example of a typical cost-effectiveness study is the West of Scotland Coronary Prevention Study (WOSCOPS) [71, 72]. The study analysed the economic efficiency in costs per life year gained from using pravastatin to prevent cardiovascular disease in men with hypercholesterolaemia. The authors estimated costs of £ 8,121 per life year gained compared to no intervention and concluded that pravastatin represents a relatively good value for money in the UK [71].

CEA-Anwendung rückläufig & Limitationen:

The application of CEA has decreased recently because most method guidances suggest the use of CUA [3]. The most significant limitations of CEA are:

- The difficulty in assessing the opportunity cost (benefits foregone) in other programmes covered by the same budget.

Abschätzung der Opp.-Kosten schwierig

- The inability to compare interventions with outcomes in different natural units (e.g., interventions with the aim to reduce severity of depression cannot be compared with an intervention aimed at improving HRQoL).

krankheits- & sektorübergreifende Vergleiche nicht möglich

- The missing consideration of broader health-related benefits because CEA restricts itself to disease-specific clinical outcomes.

nur krankheitsspezifische Endpunkte berücksichtigt

Hence, CEA cannot inform decision makers of broader resource allocations across different disease classes and beyond the healthcare sector [3].

→ keine Informationen über sektorübergreifende Ressourcenallokationen

Cost-consequence analysis (CCA) is a special form of CEA that takes a broader perspective [73]. However, in the literature, there is a debate about whether CCA is a full HEE. CCA includes multiple clinical outcomes (consequences) and compares them with costs. The CCA offers a disaggregated overview of a wide range of costs and impacts of the interventions of interest and typically includes all types of effects, including health, non-health, negative and positive effects, to patients and other stakeholders (relatives, caregivers, etc.). CCA is considered more comprehensible and practical for decision makers, as they can choose the combination of costs and impacts most relevant to their context. Health economic guidance publications recommend using CCA as an analysis instrument, especially in the case of complex interventions [74].

Kosten-Konsequenzen-Analyse (CCA): spezifische Form der CEA → breitere Perspektive & aufgeschlüsselte Übersicht über ein breites Spektrum von Kosten & Endpunkten (Konsequenzen)

A limitation of CCA is that it only gives an overview of the relative costs and outcomes without setting them in relation to a common summarising measure [75]. In addition, the arbitrary contextualisation of costs and impacts in CCA can bias the results, making the interpretation of results more subjective than for other types of HEE. [73].

Limitation: „nur" eine Übersicht über die relativen Kosten & Konsequenzen

An example of a CCA from a government healthcare perspective is the CCA alongside the INFANT study [76]. The study investigated a decision-support software developed to interpret fetal heart rate information during labour. The authors conclude that this decision-support is not associated with additional maternal or infant benefits. Furthermore, the decision-support did not result in additional costs or savings for the National Health Service (NHS) over two years.

Beispiel für CCA: INFANT-Studie (2021)

3.2.2 Cost-Utility Analysis (CUA)

Within the application of CUA, the clinical effects are converted into generic utility[11] values (utilities), which usually reflect HRQoL. Utilities incorporate the values and preferences of different health states. One of the most often used utility measures in CUA are quality-adjusted life years (QALYs). Some jurisdictions, such as the United Kingdom, require using CUA with QALYs when interventions are evaluated for funding by the NHS [77]. QALYs, as the name suggests, reflect the length of life (quantity) and the quality of life. It is a mathematical product of the number of life years gained multiplied by the HRQoL values during these years, which can range between zero (a state equivalent to death) and one (equivalent to full health) [3].

Kosten-Nutzwert-Analyse: klinischer Endpunkt wird in gesundheitsbezogene Lebensqualität (HRQoL) bzw. Nutzwert wie QALYs umgewandelt

QALYs = Lebenserwartung x Lebensqualität

HRQoL measures used to calculate QALYs are multidimensional and commonly cover the following dimensions: (i) disease state, physical symptoms/status, (ii) emotional or psychological functions, (iii) mental or cognitive functioning (iv) social functioning, and (v) perceptions of well-being [78]. The most common generic questionnaire-based instruments used to measure HRQoL[12] [3] are the Short-Form Six-Dimension, 12-Dimension, 36-Dimension (SF-6D, SF-12D, SF-36D) [80] or the EuroQoL (EQ-5D)[13]. Many coun-

fragebogenbasierte HRQoL-Instrumente: Short-Form (SF) Six-Dimension, 12-D, 36-D & EuroQoL (EQ-5D) …

[11] Utility stems from the philosophical theory of utilitarianism. In health economics, utility refers to well-being or preferences about health state profiles of individuals and society across time [49, 53].

[12] Hernandez-Segura et al. [2022] provide an overview and description of generic HRQoL measures.

[13] The EQ-5D includes health related questions for five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

… 3 Ansätze zur Bewertung von HRQoL-basierten Gesundheitszuständen

tries have derived value sets for a defined number of (EQ-5D) health states from a representative population sample [81]. When HRQoL-health states are elicited from patients during a clinical study, the population value sets are used to value those health states to calculate QALYs. Different approaches exist to value the elicited HRQoL-based health states. Most commonly, the following methods are applied: standard gamble (SG), time trade-off (TTO) and visual analogue scale (VAS) (Table 3-5).

Einbindung von HRQoL kann verzerrungsanfällig sein

A critical point of HEE integrating QoL is that this measure is self-reported or, in some circumstances, reported by relatives or caregivers. Hence, the values are prone to be biased because they are "subjective". Reported outcomes are not necessarily true (reporting bias) and may only reflect clinical outcomes to a certain degree.

QALYs repräsentieren spezifischen Gerechtigkeitsansatz

Notably, QALYs embody an implicit equity approach, which is to assign equal value to each unit of health gain, irrespective of the characteristics of the recipients, how the benefit is generated, or the reason an intervention is required in the first place ("A QALY is a QALY") [82, 83].

Alternative zu QALYs "krankheitskorrigierte" Lebensjahre (DALYs)

As an alternative to the QALYs, utility values such as "healthy life years" (HLY) [84] commonly used in CUA of public health interventions in low- and middle-income countries, "disability-adjusted life years" (DALYs) [85] or "saved young life equivalent" (SAVE) [86] can also be calculated.

QALYs ermöglichen krankheits- & populationsübergreifende Vergleiche

Generic measures, such as the QALY, enable the comparison of interventions across different diseases and populations, e.g., in the form of league tables. League tables are used to compare "competing" healthcare interventions with each other [87, 88]. League tables are (cost-utility) rankings that show the relative cost per QALY for different healthcare interventions in ascending order [63]. Decision makers and policy makers sometimes use league tables as a policy guiding tool for a comprehensive assessment of health expenditures and as a tool for national healthcare planning. League tables for priority setting need to be handled with care due to the potential fallacies [87, 89].

"League Table" = Rangliste von Interventionen zur Steuerung des Gesundheitssystems

Table 3-5: Overview of approaches for measuring preferences and deriving utility values

Approach	Description
Standard gamble (SG)	A patient is offered two alternatives: an intervention with a guaranteed health state, e.g., a patient has a certain chronic state and lives for ten years, or an intervention with a gamble regarding the health outcome. The gamble has a probability p of the best possible outcome (optimal health = 1) and probability (1-p) of the worst possible outcome (e.g., immediate death = 0). Probability p is varied until the respondent is indifferent between the two alternatives. The parameter p is then the preference value for the described health state [90, 91].
Time trade-off (TTO)	A patient is asked to choose between two alternatives: her remaining life expectancy in the state "alive with impaired/chronic condition" and a shorter life span in "perfect" health. The time is varied until the patient is indifferent between the two alternatives. At this point, the required preference value for the state "alive, impaired/chronic condition" is the ratio of the life expectancy in the "alive, impaired/chronic condition" state and the shorter life span in "perfect" health [90, 91].
Visual analogue scale (VAS)	A patient is asked to rate a set of presented health states on a thermometer-like rating scale by indicating the relative positions of each health state. The scale usually consists of a single line with 100 points at one end, indicating an optimal health state, and 0 at the other, indicating the worst health state or death. The intervals or spacing between the placements correspond to the difference in preference as perceived by the subject [90, 91].

Bsp. für CUA: JUPITER-Studie (2010)

An example of CUA is the HEE based on the JUPITER trial. This CUA looked at the long-term cost-effectiveness of rosuvastatin (20 mg) compared with no active treatment in patients at a higher risk of cardiovascular diseases (CVD). The authors estimated that rosuvastatin therapy was cost-effective over a lifetime horizon at a WTP threshold of $ 30,000 per QALY [92].

3.2.3 Cost-Benefit Analysis (CBA)

Kosten-Nutzen-Analyse: Umwandlung von Kosten & Nutzen in Geldeinheiten

In this analysis, all consequences of relevant interventions, i.e. costs and effects, are converted into monetary units. CBA is popular with policy- and decision makers as this approach is more traceable. However, CBA is not extensively used in health technology assessment by HTA institutions as the task of assigning monetary values is not trivial [93]. Theoretically, economists advocating CBA prefer prices that are "formed" in supposedly perfectly competitive markets [3].

CBA nicht weit verbreitet in HTAs

Schritte einer CBA:

The following steps are typical for a CBA:

- As a first step, clinical outcomes, utility values such as QALYs or DALYs or avoided complications must be translated into monetary units.
  Nutzen in Geldeinheiten umwandeln
- Secondly, all relevant costs associated with the interventions are derived.
  Interventionskosten herleiten
- In the third step, the relevant costs are balanced against the monetary benefits (effects) to calculate a monetary net benefit/net cost[14], benefit-cost-ratio or return on investment (ROI).
  Kosten & monetärer Nutzen gegenüberstellen

If two or more competing interventions are compared, the intervention that provides the largest net benefit is often recommended.

CBA → Vergleich von Intervention & Policies über Politikbereiche hinweg theoretisch möglich

Proponents of CBA in the health economic literature assert that CBA follows the central economic concept in its pure form: the opportunity cost approach (see Chapter 3.1.2 Economic Costs and Opportunity Cost Approach). CBA offers an overview of all costs and effects of the interventions in the same accounting unit. Therefore, CBA is considered more practical for decision and policy makers or systems with a shared budget. CBA enables policy makers to compare policy interventions and allocate resources across policy areas such as social care, justice, or the healthcare sector.

3 Ansätze zur monetären "Bewertung" von Kosten & Nutzen: „Marktpreise"/Human Capital Approach, „Offenbarte" & „Geäußerte" Präf.

Health economists commonly use three approaches to assign monetary values to costs and effects (benefits) of health care interventions: (i) Market prices or the human capital approach, or in the absence of market prices, (ii) the revealed or (iii) stated preferences approach to calculate a "shadow price". Revealed and stated preference approaches are mainly used to assign monetary values to intervention benefits (outcomes) by eliciting willingness to pay, willingness to accept (WTA), or willingness to avoid harm values from the target population. Both approaches approximate the monetary value of the income maintained by the reestablished healthy state of the patient [3].

geäußerte Präf. → kontingente Bewertungsmethode: Befragungen von Pat. zu hypothetischen Auswahlszenarien von Interventionen → Zahlungsbereitschaft für die Interventionen

One common method to elicit *stated* preferences is the contingent valuation approach. The contingent valuation approach uses survey methods and presents respondents with hypothetical choice scenarios. Respondents, such as payers or patients, are asked to consider what they would be willing to pay for the intervention benefits. The responded amount reflects the sacrificed amount of money in terms of other commodities. The contingent valuation approach is mainly used to elicit the WTP for studies in publicly financed healthcare systems. In these systems, prices do not exist or do not reflect actual costs [94]. However, the contingent valuation approach potentially suffers from the same biases surveys or self-reported outcomes suffer: respondents ignoring income constraints, strategic behaviour, or protest answers [3].

[14] Difference between the costs and effects in monetary units.

One common method to elicit *revealed* preferences is the wage-risk approach. If two jobs are identical regarding the required skills, one job has a higher (health) risk for injuries and this job pays more, then the value reflects the monetary amount of the risk [3]. Instead of the job example, health interventions can be used to draw the connection to the medical context. However, such choices are dependent on the context and system characteristics. A person in material deprivation is more likely to accept a job with a higher risk than a person without material deprivation. Nevertheless, health economists emphasise the strength of the revealed preference approach, such as the wage-risk approach, because it reflects actual choices.

offenbarte Präf. → "Wage-Risk"-Ansatz: Entscheidung zwischen zwei Alternativen mit unterschiedlichen Risiken & Outcomes

Limitation: kontextabhängig

The main difference between these two approaches can be summarised as follows: The stated preference approach reflects what people say about a state of health or a commodity regarding their preferences, and the revealed preference approach reflects what people actually do in a situation where they have to choose between alternatives. Both approaches can also be used to estimate economic costs a patient has to bear or would be willing to pay to get the intervention. For example, the contingent valuation approach assigns an economic value to the time a patient spends using an intervention or economic benefits resulting from the cure of an illness. Patient time includes time to admission, travel, waiting, and treatment time, which can be substantial.

Unterschied zwischen Ansätzen: was Pat. über einen Gesundheitszustand sagen (geäußerte Präf.) vs. was Pat. in einer Entscheidungssituation tatsächlich tun (offenbarte Präf.)

Table 3-6: Approaches to assign monetary values to costs and effects (benefits) of health care interventions[15]

Approach		Description	Example
Market prices available	Market prices	Current (selling or buying) price for a good or service determined by supply and demand in a (perfectly competitive) market	E.g., market price for a medical device
	Human capital approach	Using wages to value productivity gains from the input "labour". This method assumes that an individual's life has a value equal to the produced commodities (productivity).	Suppose an intervention improves a patient's recovery from illness or an accident. In that case, the added (indirect) benefit might be returning to work sooner, which can be valued in terms of earning gains.
Market prices not available	Stated preferences	Stated preferences are preferences that people give in response to questions.	How much are you willing to pay or accept for being in health state A, and how much are you willing to pay/to accept for being in health state B?
	Revealed preferences	Revealed preferences are preferences that people reveal through their choices/behaviour.	Which did you in fact choose, health state A or B, and how much were you willing to pay/accept?

An example of CBA is the HEE of the Stand More AT Work (SMArT Work) intervention, designed to reduce sitting time [95]. The intervention group received a height-adjustable workstation with supporting behaviour change strategies and the control group continued with usual practice. Cost-benefit estimates showed a net saving of £ 1,770 (95% CI: £ 354.40, £ 3,895.04) per

Bsp. für CBA: Stand More AT Work-Studie (2020)

[15] The stated and revealed preferences approaches do also play a role in eliciting utility values in CUA. In the CUA context with two intervention options A and B, the questions to elicit utilities for each alternative are differently formulated. Question for stated preferences in the CUA context: Do you prefer health state A or B? Question for revealed preferences in the CUA context: Which health state, A or B, did you in fact choose? Furthermore, both approaches play a role in estimating *societal* ICER thresholds in the sense of WTP thresholds (i.e., ICER thresholds reflecting a societal perspective, see Chapter 3.4.3 Universal ICER Thresholds and Societal Willingness to Pay ICER Thresholds (Societal WTP Thresholds))

employee because of productivity increase. Munir et al. [2020] conclude that SMArT Work provides supporting evidence on the cost benefits of reducing sitting time at work.

Praktikabilität & Validität von CBA aufgrund methodologischer Limitationen fraglich

CBA is rarely used in HTA practice due to its methodological limitations [63]. In theory, proponents of CBA claim that CBA captures opportunity cost in a broader sense than CEA. However, in practice, determining opportunity cost within CBA is very challenging to operationalise. Efficient market values (prices) as shadow prices are distorted because markets do not behave as Neo-classical economic theory suggests (see Chapter 3.1.3 on Efficiency, Utilitarianism, Welfarism, and Extra-Welfarism and Table 3-4) [63, 67]. Furthermore, valuation methods, such as contingent valuation, are time-consuming.

3.2.4 Overview and Summary of Evaluation Types

zusammenfassende Übersichtstabelle

Table 3-7 provides an overview of each HEE, including the measurement units regarding the effects and costs, and summarises when the application of each type of evaluation is recommended.

Table 3-7: Summary and overview of health economic evaluation types based on Drummond et al. [2015], own depiction

Type of evaluation	Measurement unit of effects	Measurement unit of costs	Recommended …
Cost-effectiveness analysis	Natural units: ■ Disease-specific clinical endpoints: cholesterol level, cardiovascular events, pain, blood glucose levels, severity of depression, severity of psoriasis etc. ■ Generic clinical endpoints: progression-free survival, morbidity, life years saved or lost or mortality	Monetary units	… if decision or policy makers want to achieve a very specific health objective or to consider only a limited range of interventions within a disease class
Cost-utility analysis	Utility measures: ■ Quality-adjusted life years (based on EQ-5D, SF-6D, SF-12D, SF-36) ■ Healthy life years ■ Disability-adjusted life years ■ Save young life equivalent	Monetary units	… if decision or policy makers want to make a comparison of interventions across different diseases/populations for a comprehensive assessment of health expenditures and as a tool for national healthcare planning
Cost-benefit analysis	Monetary units	Monetary units	… if decision or policy makers want to make a comparison of different policy interventions, include also non-health effects and allocate resources beyond the healthcare domain (social care, justice, education sector)

Abbreviations: HRQoL … Health-Related Quality of Life, SF … Short-Form

3.3 Incremental Cost-Effectiveness Ratio and Thresholds

3.3.1 The Incremental Cost-Effectiveness Ratio

ICER Kernkonzept in CEA/CUA:

zusätzliche Kosten pro Gesundheitseffekt

The incremental cost-effectiveness ratio (ICER) is the primary outcome of a CEA or CUA. This ratio represents the additional costs per additional unit of health effect comparing (at least) two interventions.

Formally, the ICER is depicted by the following equation:

$$ICER = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} \quad (1)$$

C … Kosten der jeweiligen Intervention

E … Effekt der jeweiligen Intervention

ΔC … Kostenunterschiede

ΔE … Effektunterschiede

C_2 and E_2 are the cost in monetary units, and the effect (natural units or utility measures) of the intervention of interest, and C_1 and E_1 are the cost and effect of the comparison intervention. The components in the numerator have the same unit (cost component in monetary units) and the components in the denominator have the same unit (health effect). Otherwise, different interventions cannot be compared. Usually, an already cost-effective comparator, which also reflects the SOC in the same disease class, is used for comparison. Only then, decision makers get the correct information of the outcome measures to efficiently use the resources and obtain the highest health benefits [12].

Nettonutzen ist eine Alternative zu ICER

λ repräsentiert Opp.-Kosten (WTP, Preisobergrenze etc.)

Another optional outcome magnitude is the net benefit (NB). The NB is a relevant outcome measure in all three types of HEE with λ being a specific willingness to pay, ceiling price, or estimated threshold for a unit of effect[16] representing opportunity cost. In the case of CBA, instead of the effect difference (ΔE), the benefit difference (ΔB) is used and λ equals 1.

$$\begin{aligned} NB &= \lambda * (E_2 - E_1) - (C_2 - C_1) \\ &= \lambda * \Delta E - \Delta C \end{aligned} \quad (2)$$

CBA-Kennzahlen: Nutzen-Kosten-Verhältnis bzw. „Return on Investment“

In the case of CBA, two other relevant outcome measures are the benefit-cost ratio (BCR) and the return on investment (ROI):

$$BCR = \frac{B_2 - B_1}{C_2 - C_1} = \frac{\Delta B}{\Delta C} \quad (3)$$

$$ROI_{single} = \frac{B - C}{C}$$

$$ROI_{comp} = \frac{(B_2 - B_1) - (C_2 - C_1)}{(C_2 - C_1)} = \frac{\Delta B - \Delta C}{\Delta C} \quad (4)[17]$$

Table 3-8 summarises the relevant outcomes of the different types of HEE.

[16] Depending on the method and type of threshold, λ is either a k-threshold (opportunity cost of health expenditures in a fixed budget setting) or a v-threshold (societal WTP or opportunity cost in a flexible budget setting) (see distinction in Section 3.3.4 on ICER Threshold Methods and Fixed versus Flexible Budget Constraints).

[17] ROI_{single} gives the return of one alternative and ROI_{comp} gives the comparative return of two alternatives.

Table 3-8: Overview of outcomes in different types of health economic evaluations

Analysis	Outcome	Formula	Description
CEA/CUA	Incremental cost-effectiveness ratio (ICER)	$ICER = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E}$	The ICER is a measure of the additional cost per additional unit of health gain of one intervention in comparison with an alternative [13].
CEA/CUA/ CBA	Net benefit (NB)	$NB = \lambda * (E_2 - E_1) - (C_2 - C_1)$ $= \lambda * \Delta E - \Delta C$	The net benefit is a measure representing the value of an intervention when a willingness to pay for a unit of effect (λ) is known [96]. For CBA, E = B, and λ is 1.
CBA	Benefit-cost ratio	$BCR = \frac{B_2 - B_1}{C_2 - C_1} = \frac{\Delta B}{\Delta C}$	The benefit-cost ratio is the monetised benefits or benefit difference of two competing interventions divided by its cost (difference) [97].
CBA	Return on investment	$ROI_{single} = \frac{B - C}{C}$	The ROI is used to evaluate the efficiency of one or several different interventions and measures the amount of "economic return" relative to its cost. The ROI is usually expressed as a percentage [93]. E.g. a ROI of 1.5 (150%) means that € 1 invested/ spent results in an additional payoff of € 1.5.
		$ROI_{comp} = \frac{(B_2 - B_1) - (C_2 - C_1)}{(C_2 - C_1)}$ $= \frac{\Delta B - \Delta C}{\Delta C}$	

Abbreviations: CBA … cost-benefit analysis, CEA … cost-effectiveness analysis, CUA … cost-utility analysis, ICER … incremental cost-effectiveness ratio, ROI … return on investment

3.3.2 General Decision Rules in Health Economic Evaluations

Entscheidungsregeln bei CBA:

Net-Benefit > 0 → Erstattung/ Implementierung; Net-Benefit < 0 → keine Erstattung/ Implementierung

In a properly conducted CBA, the decision rule on whether resources are optimally used in an economic sense is straightforward: If the net benefit of the intervention of interest is positive compared to an already established alternative, it should be reimbursed or implemented instead. The intervention should be rejected if the net benefit is negative and only efficiency criteria are relevant in the reimbursement process. In mathematical terms, the following decision rules for the NB in a CBA apply:

$$\begin{aligned} Net\ monetary\ benefit &= \lambda * (B_2 - B_1) - (C_2 - C_1) > 0 \\ &= \lambda * \Delta B - \Delta C > 0, \qquad with\ \lambda = 1 \end{aligned} \tag{5}$$

Inequality (5) can be rearranged to depict the net health benefit instead of the net monetary benefit:

$$\begin{aligned} Net\ health\ benefit &= (B_2 - B_1) - \frac{(C_2 - C_1)}{\lambda} > 0 \\ &= \Delta B - \frac{\Delta C}{\lambda} > 0, \qquad with\ \lambda = 1 \end{aligned} \tag{6}$$

However, as described above, CBA is rarely used in HTA practice due its methodological limitations [63].

Entscheidungsregel-Matrix im Falle von CEA & CUA

In the case of CEA and CUA, the decision rules are more "complex". Figure 3-1 shows the cost-effectiveness decision rule matrix. The matrix depicts the decision rules depending on the comparative degree of effectiveness and costs analysed in CEA and CUA. Given a fixed budget or resources, if a new intervention achieves better or equal results at lower costs[18] than an already

[18] In technical terms: the new intervention is more effective, has less costs compared to the comparator and is therefore technically or productively efficient.

implemented or reimbursed intervention (A1 and A2), then decision makers should substitute the more costly and less effective intervention. If a new intervention achieves better results at the same costs (B1), then decision makers should also implement the new intervention.

neue Intervention technisch ineffizient → Ablehnung einer Erstattung aus ges.ök. Sicht

If a new intervention is more or equally costly and less effective (C3 and B3), i.e. technically or productively inefficient, then the decision to reject should also be clear on efficiency grounds. The same applies to an equally effective and more costly new intervention. The case of indifference, equally effective and equally costly, is deemed unlikely.

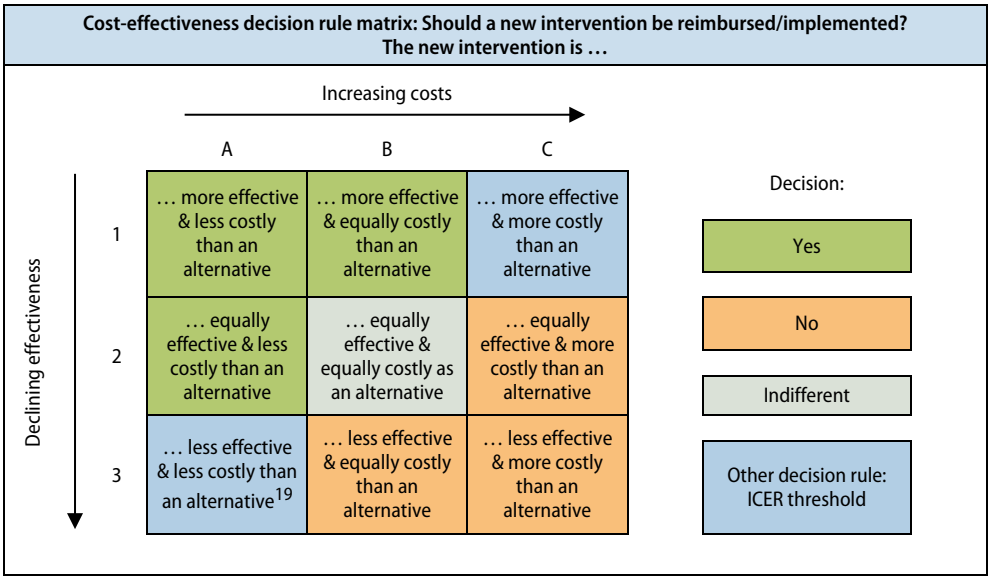


Figure 3-1: Cost-effectiveness decision rule matrix based on Donaldson et al. [2002], own depiction

In practice, many novel health care interventions are both cost-increasing and health-enhancing, rather than cost-decreasing or clinically ineffective [11]. If a new intervention is either more effective and more costly or less effective (C1) and less costly compared (A3[19]) to an alternative, then another decision rule must be consulted. By using equation (1) for the ICER, the relevant decision rule becomes the following:

neue Interventionen meist kosten- & gesundheitssteigernd → andere Entscheidungsregel relevant:

ICER < λ

$$ICER = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E} < \lambda \qquad (7)$$

Inequality (7) indicates that the ICER needs to be smaller than a certain ceiling value (λ) – the ICER threshold. Inequality (7) can be rearranged to arrive at the incremental net monetary benefit (INMB) or incremental net health effect (INHE).

$$INMB = \lambda * \Delta E - \Delta C > 0$$
$$INHE = \Delta E - \frac{\Delta C}{\lambda} > 0 \qquad (8)$$

[19] The interpretation of A3 is a bit more nuanced than just consulting an ICER threshold, as the intervention represents a trade-off between saving money, rather release resources including dismissing staff, and accepting worse health outcomes.

These two mathematical expressions indicate that an intervention can be considered cost-effective if it results in a positive INHB or INME.

Entscheidungen in Fällen C3 & A1 setzen eine Kontextualisierung voraus → Schwellenwert

Hence, in the cases C3 and A1, a decision can only be made if the ICERs are contextualised. Contextualisation includes considering the budget context and the consultation of reference values such as ICER thresholds, a ceiling price, or other decision-making criteria. The next section takes a closer look at the ICER thresholds.

3.3.3 The ICER Threshold

General Characteristics of an ICER Threshold

allgmeine Definition von Schwellenwerten

A common definition for a threshold in the health economic literature is the following by Claxton et al. [2015]:

Schwellenwert spiegelt Opp.-Kosten wider

> *"Given that NICE has no influence on the level of the NHS budget, its decisions need to consider that budget as a fixed constraint. Therefore, the threshold should reflect the opportunity costs, in terms of health forgone, resulting from the imposition of additional costs on the NHS. When NICE issues positive guidance for a new intervention which imposes additional costs on the system, the resources required to deliver it must be found by disinvesting from other interventions and services elsewhere. This displacement of existing services will result in health decrements for other types of individuals. Thus, the threshold represents the additional cost that has to be imposed on the system to forgo 1 QALY's worth of health through displacement."* – Claxton et al. [2015, p. 3]

Opp.-Kosten als Schwellenwert: reale Ressourcen vs. monetäre Darstellung

Hence, one of the main characteristics of the ICER threshold is that the threshold is an approximation of opportunity cost [98, 99]. Opportunity cost should always depict real resources and not just distorted prices (see Section 3.1.2, 3.1.3, and Table 3-4). Common definitions of ICER thresholds often conflate temporarily scarce real resources with politically limited monetary funds within a budget period. The budget and its derived threshold[20] are frequently interpreted in monetary terms rather than as a representation of available economic resources. The monetary budget merely represents these resources, as it emerges from their economic interaction.

Budgetgrenzen im Gesundheitswesen: Politische Entscheidungen vs. reale Ressourcenverfügbarkeit

It may be correct that the health budget in certain systems is limited or fixed. However, the limitation is not a natural constraint but a political constraint (national fiscal rules regarding new or accumulated debts such as the "Schuldenbremse" in Germany or EU convergence criteria). Government spending and funds are limited by the scarcity of real resources. If the government or public bodies have enough funds and want to buy something, but no one wants to sell it, then it cannot spend money. Vice versa, if the economy has excess capacity, but the government is self-limiting in spending, the whole economy is underutilised. Therefore, if a decision maker wants to know the actual resources, it would be necessary to have an accounting system representing real resources available.

[20] There is a close link between the budget and threshold. As Culyer [2015] puts it: *"One way of looking at the threshold is nonetheless as a demand concept – an implication of a collective willingness to pay for health as expressed by the size of the health budget".*

To highlight the distinction between real economic resources and monetary funds, we suggest the following alternative definition of the ICER threshold:

Neudefiniton des Schwellenwerts:

Fokus auf reale Ressourcen & deren Opportunitätskosten

> *An ICER threshold is a cut-off point or reference value below which a novel intervention is cost-effective or efficient (i.e. maximises total health from available resources). The threshold should reflect the opportunity costs of health forgone resulting from deploying additional* ***real economic resources*** *from elsewhere. These resources can be temporarily acquired only by taking them away from other interventions and services.*

Overall, the ICER threshold is a dynamic, context- and time-dependent concept [4, 12, 99]. The definition, logic, and the threshold amount depend, among many other things, on …

verschiedene Determinanten des Schwellenwerts:

- the type of the budget (fixed or flexible budget), its changes over time and the interaction of economic resource inputs,
- whether the competing alternatives focus on the same disease class,
- the healthcare system characteristics and health insurance system,
- the organisation of health care programmes and funded interventions,
- changes in the productivity (of health care services).

Budgettyp,

Indikation,

Gesundheitssystem-charakteristika,

Produktivität

Although the budget type is not the only threshold determinant, whether it is politically fixed or variable, has a major impact on the ICER threshold, its logic, interpretation, and the decision rules regarding reimbursement. Therefore, depending on the budget setting, the ICER threshold can be a choice or flexible variable.

fixes vs. flexibles Budget hat Auswirkungen auf die Logik und Interpretation der Schwellenwerte

The following subsections will detail how the relationship between the type of budget-setting and the ICER threshold arises. We also discuss the different interpretations of the ICER thresholds and the ICER's logic depending on the budget setting.

Budgettypen & deren Auswirkungen im nächsten Kapitel

A Fixed Budget Setting and Flexible ICER Thresholds

General Characteristics and Assumptions in a Fixed Budget Setting

If the health care budget is fixed (e.g., by annual parliament decisions), which limits and fixes also the resources, a variable ICER threshold value is required. In this case, the choice variable is the budget, while the threshold is flexible.

fixes Budget → variable Schwellenwerte als logische Konsequenz

Cleemput et al. [2008] define the ICER threshold in a fixed budget setting in the following way:

Definition nach Cleemput et al (2008):

Schwellenwert als Effizienzkriterium & Grenze der Gesundheitsmaximierung bei fixem Budget (Neoklassische Theorie)

> *"In neo-classical welfarist economic theory it can be shown that, under a fixed budget constraint, an ICER threshold value can be defined above which interventions do not improve efficiency (i.e. maximise total health from available resources) and below which they do improve efficiency. The ICER threshold value is the ICER of the last intervention in a league table that would still (fully or even partially) be financed from a given fixed budget."* – Cleemput et al. [2008, p. iii]

The league table or "bookshelf" approach is a stylised tool to evaluate efficiency and define the threshold in a reimbursement decision on a new intervention [99]. The league table can be used[21] to compare "competing" healthcare interventions with each other as already outlined in the Chapter on CUA (3.2.2) [87, 88]. A league table is a (cost-utility) ranking that shows the rela-

Effizienzbestimmung durch „League Tables" in der Theorie möglich: League Tables: effizientes Kosten-Nutzen-Ranking

[21] Whether the league table approach is carried out in jurisdictions in reality is not up for discussion here. The focus is on explaining the economic logic.

tive cost per effect for different healthcare interventions in ascending order [63]. Within the theoretical league table approach, the ICER threshold value is revised every time a positive reimbursement decision of a new intervention is made. A situation with a politically fixed budget setting and fixed resources is a textbook example addressing questions of static technical efficiency and static opportunity cost considerations.

League-Table-Ansatz setzt einige restriktive Annahmen voraus

Certain strict assumptions must be met for this approach to work properly. Otherwise, one cannot derive an ICER threshold in a fixed budget setting [12]. These strong assumptions are derived from Neoclassical welfarist theory, which in turn rests on the philosophical theory of utilitarianism outlined in Chapter 3.1.3 [49].

Übersicht der 6 Annahmen in Tabelle 3-9

Table 3-9 gives an overview of the main assumptions of the ICER threshold in a fixed budget setting based on the report and publication of Cleemput et al. [2008]. The assumptions should not be understood in a prescriptive way but as the underlying modus operandi of HEE in a fixed budget setting.

Table 3-9: Basic assumptions of health economic evaluations and ICER thresholds in a fixed budget setting

#	Assumption	Description
1.	Politically fixed healthcare budget over a specific period	Jurisdictions define budgets over a financial year based on politically set household regulations and laws. A fixed budget means that the politically established budget cannot be increased or overspent within a given period (financial year). This does not mean that the budget will remain constant over time.
2.	Constrained maximisation of health outcomes only	The primary goal of decision or policy makers is to maximise health outcomes within a politically fixed healthcare budget or specific threshold (in mathematical terms: constrained optimisation).
3.	Full information on costs and effects	Information on costs and effects of all available health care interventions is available.
4.	Perfect divisibility	All components of the intervention or programme can be combined in various ways, like modules in a modular system, including the option to use only selected parts.
5.	Independence of healthcare programmes/interventions	The (compared) healthcare programmes/interventions are independent of each other.
6.	Constant returns to scale	Changing the scale of the intervention or programme does not affect its ICER.

League Table wird bei „neuem" Interventionsvergleich herangezogen; Entscheidungsregeln zur Auswahl zwischen konkurrierenden (neu vs. alt) Interventionen:

If all assumptions in a fixed budget setting were satisfied, the interventions listed in the league table would represent the optimal combination of current interventions. When a reimbursement decision for a new intervention is required, the league table serves as a reference point. The ICER of the new intervention ($ICER_{new}$) is then compared with the ICER of the last cost-effective, currently funded intervention ($ICER_{last}$) in the league table [12]. The $ICER_{last}$ is always the current decisive ICER threshold value. Two mutually exclusive decision rules apply when comparing the ICERs of the two alternate interventions:

ICER neu > ICER alt → Intervention nicht kosteneffektiv → keine Erstattung

- If $ICER_{new} > ICER_{last}$, the new programme is not cost-effective, and decision makers should not accept the intervention for reimbursement[22]. Otherwise, the reimbursement of the new intervention would displace potential life years.

[22] This decision rule complies with the situations B3, C2, and C3 in Figure 3-1.

- If $ICER_{new} < ICER_{last}$, the new intervention would increase the relevant health outcome. Furthermore, all outcomes are maximised given the fixed budget, and decision makers should accept the intervention for reimbursement while disinvesting the former last cost-effective financed intervention in the league table. The ICER of the new intervention is now also the threshold for the subsequent decision on whether the following new intervention is efficient. The case of $ICER_{new} = ICER_{last}$ complies with the indifferent situation B2 in Figure 3-1. This situation is deemed unlikely in practice.

ICER neu < ICER alt → Intervention kosteneffektiv → Erstattung

Many of the assumptions are clearly not satisfied in reality. First and foremost, decision and policy makers do not have all the information on all health care interventions at hand [100]. Consequently, decision and policy makers may not be able to derive the necessary league tables from comparing all the "competing" interventions[23] [63, 87, 88]. In practice, no decision or policy maker calculates opportunity cost, i.e. the flexible ICER threshold, within a fixed budget setting by using the league table approach. For example, although the British NHS system has a fixed budget, it also has a fixed ICER threshold. Estimation techniques exist to approximate opportunity cost in a fixed budget setting. (see Section 3.4.1 on Empirical ICER Thresholds in a Fixed Budget Setting: Opportunity Cost Threshold Approach).

praktische Einschränkungen des League-Table-Ansatzes u. a. aufgrund von hohem Informationsbedarf

→ Annäherungen an Opp.-Kosten durch Schätzverfahren

A Fixed Budget Setting and Different Levels of Comparison

So far, no distinction has been made regarding whether the comparison of competing alternatives focused on the same disease class or interventions for distinct diseases and populations. Three cases must be distinguished:

verschiedene Vergleichsebenen:

Case 1: Comparison of two competing interventions from the same disease class. The league table represents the current, efficient bundle of disease-specific interventions. The comparison is between the new intervention and the current SOC ("gold standard") for the same indication.

Interventionsvergleich innerhalb einer Krankheitsklasse

Case 2: Comparison of two competing interventions from distinct disease classes or populations with a joint league table in the context of a fixed budget for the healthcare system. The joint league table includes the currently efficient bundle of different interventions in the healthcare system.

krankheitsübergreifender Interventionsvergleich

Case 3: Comparison of two competing interventions or policies from different policy sectors with a joint league table for the whole jurisdiction in the context of a fixed budget for the jurisdiction. The joint league table for the whole jurisdiction includes all currently efficient policies and interventions.

politikfeld- bzw. sektorübergreifende Interventionen

These three cases additionally determine whether a CEA or CUA is an adequate evaluation tool[24]. In the first case, applying a CEA or CUA is possible. However, CUA is only an option if a generic measure for the population is available. In the second case, CUA is the only option. Comparisons in the third case go beyond the healthcare sector and include, for example, the social

Vergleichsebene bestimmt Methodenwahl & Messbarkeitsanforderungen

[23] A description of the league table is in section 3.2.2 Cost-Utility Analysis. Below is an introductory example of how league tables work. The example in Cleemput et al. [2008] served as a basis. Briggs and Gray [2000] and Thokala et al. [2018] provide more in-depth examples of how league tables work.

[24] CBA is technically also an option in all three comparative cases. However, ICER thresholds are not relevant in CBA with a fixed budget.

care, educational, and justice sectors. Comparing interventions across different policy domains requires either a common measure (money as in CBA) or knowledge of society's willingness to trade health gains for benefits in other domains [102].

sektorale Budgetgrenzen führen zu unterschiedlichen Optimierungsansätzen

In cases 1 and 2, a fixed budget exclusively for the healthcare sector guides the health economic optimisation process and, consequently, reimbursement decisions. The interventions are substitutional, meaning that a new intervention possibly replaces an already reimbursed intervention. Any "released" resources due to increased technical efficiency can be used for other purposes. Case 3 is technically equivalent to cases 1 and 2. The only difference is the assumption that all relevant jurisdictional policy sectors and the associated bundle of policies and interventions have a joint budget.

Example

League-Table-Beispiel: Schwellenwertbestimmung bei fixem Budget

The following example illustrates the use of league tables in combination with a flexible ICER in the context of a fixed budget. The example is embedded in a CUA setting with a generic utility measure in a specific disease class (diseases of the circulatory system).

3 Interventionen (A, B & C) im Kontext einer Erkrankungen des Kreislaufsystems

Consider three interventions focussing on diseases of the circulatory system[25]. Each intervention treats a slightly different subpopulation but can also overlap population-wise as these interventions could be cumulative or complementary in a treatment path. Intervention A provides eight additional QALYs, B 15 additional QALYs, and C 5 additional QALYs, each initially compared to an adequate comparator. The additional costs (incremental costs) are € 150,000 for A, € 300,000 for B, and € 120,000 for C. The target population comprises 15 patients for A, 20 for B, and 10 for C. The healthcare budget for diseases of the circulatory system is € 3,000,000[26].

Schrittweise ICER-Berechnung mit Gesamtkosten & -effekten von A, B & C

In the first step, the ICER is calculated by dividing the additional costs by the extra effect. Then, the interventions are ordered according to the ICER in descending order. A smaller ICER indicates that the intervention is more cost-effective. The total incremental costs are calculated by multiplying the number of relevant patients with the additional cost. The total incremental effectiveness is calculated similarly by multiplying the number of relevant patients by the additional effect. Table 3-10 summarises the results of these steps.

Table 3-10: Example: Current league table with three established interventions

Intervention	# of relevant patients	ΔC	ΔE	ICER = ΔC/ΔE	Total incremental effectiveness (# of relevant patients × ΔE)	Total incremental cost (# of relevant patients × ΔC)	Budget impact in current period	Funded (%)
A	15	150,000	8	18,750	120	2,250,000	1,000,000	Yes (100%)
B	20	300,000	15	20,000	300	6,000,000	1,800,000	Yes (100%)
C	10	120,000	5	24,000	50	1,200,000	500,000	Yes (40%)
						A + B + C =	∑ 3,300,000	

ICER threshold of the current league table

[25] Some numbers of the Cleemput et al. [2008] example were adjusted.

[26] The numbers are fictional. In 2008, € 1.3 billion were spent in the acute inpatient sector for cardiovascular diseases (ICD-10 I05 to I79) in Austria [103].

(Teil)Erstattung von Intervention C definiert „bestehenden" ICER-Schwellenwert

The total budget impact in the current period of the three interventions is assumed to be € 3,300,000. The difference between the budget (€ 3,000,000) and the budget impact (€ 3,300,000) is negative (- € 300,000). Interventions A, B, and only part of C (40%) can be financed with this budget (last column in Table 3-10). The ICER of intervention C (€ 24,000) is also the current ICER threshold ($ICER_{last}$).

neue Intervention D: ICER-Vergleich zwischen Intervention D & bestehendem Schwellenwert von C

When a new intervention (D) is introduced to the market, and a decision maker wants to make a reimbursement decision, the ICER of the new intervention must be compared with the current ICER threshold (Table 3-11) – the ICER of C ($ICER_{last}$). Let us assume that the new intervention offers treatment to 12 patients, has an incremental cost of € 130,000, and an incremental effect of 6 QALYs[27]. The budget impact of intervention D is assumed to be € 700,000 in the current budget period. The resulting ICER is smaller than the initial ICER of C (€ 24,000 > € 21,667), indicating that intervention D is more cost-effective than C.

Table 3-11: Example: League table with a new intervention

Intervention	# of relevant patients	ΔC	ΔE	ICER = ΔC/ΔE	Total incremental effectiveness (# of relevant patients × ΔE)	Total incremental cost (# of relevant patients × ΔC)	Budget impact in the budget period	Funded (%)
A	15	200,000	8	18,750	120	2,250,000	1,000,000	Yes (100%)
B	20	400,000	15	20,000	300	6,000,000	1,800,000	Yes (100%)
C	10	200,000	5	24,000	50	1,200,000	500,000	No
				>		A + B + C =	∑ 3,300,000	
D	12	130,000	6	21,667	72	1,560,000	700,000	Yes (29%)
						A + B + D =	∑ 3,500,000	

New intervention
Displaced/disinvested intervention

Effizienzsteigerung durch partielle Finanzierung der Intervention D

Implementing intervention D up to part of the remaining available budget (€ 200,000) and the displacement (disinvestment) is efficient. The partial financing of intervention D (29%) increases the total number of additional QALYs. The ICER of the last cost-effective intervention is the ICER of intervention D (€ 21,667). Any subsequent new intervention must be compared with this $ICER_{last}$ [12]. The result of the calculation is depicted in Table 3-12.

Table 3-12: Example: New league table with new ICER threshold ($ICER_{last}$)

Intervention	# of relevant patients	ΔC	ΔE	ICER = ΔC/ΔE	Total incremental effectiveness (# of relevant patients × ΔE)	Total incremental cost (# of relevant patients × ΔC)	Budget impact in the budget period	Included (%)
A	15	200,000	8	18,750	120	2,250,000	1,000,000	Yes (100%)
B	20	400,000	15	20,000	300	6,000,000	1,800,000	Yes (100%)
D	12	130,000	6	21,667	72	1,560,000	700,000	Yes (29%)
						A + B + D =	∑ 3,500,000	

New ICER threshold of the new league table ($ICER_{last}$)

[27] The cost and effect increments could be either a result of the comparison of intervention C and D if C is the current SOC of D or a comparison between D and another adequate comparator of D. It is only important that the initial ICER of intervention C ($ICER_{last}$) is compared with the "new" ICER of Intervention D.

Budget determiniert ICER-Schwellenwert & Erstattungs- bzw. Implementierungsgrad der Interventionen

In the league table example, the available fixed budget for the budget period was smaller than the needed budget to fully implement interventions A, B, and D. If the total budget impact had been smaller than the available budget of € 3,000,000, D could have been fully financed. Intervention D could also have been fully funded if the budget had exceeded € 3,500,000. Any "released" funds or additional funds could have been used to implement (parts of) the displaced intervention C if the population or indication differed from intervention D's or to fund other interventions. This would change the ICER threshold again to the ICER of C or another intervention decision makers wish to fund. This example shows that the ICER threshold depends on the budget.

League-Table-Ansatz ermöglicht sektorübergreifende Interventionsvergleiche, aber meist nicht praxistauglich

The presented example could be modified to represent the other presented cases or levels of comparison mentioned in the previous subsection (see A Fixed Budget Setting and Different Levels of Comparison). One could compare interventions from different disease classes in a healthcare system (diseases of the circulatory system vs. neoplasms) or competing policies from different policy sectors (poverty alleviation vs crime prevention vs crime "control"/law enforcement [104]). However, in practice, this approach is not implemented due to limited data availability and extensive information requirements.

Summary and Implications of a Fixed Budget Setting on the ICER Threshold

Implikationen des Schwellenwerts & League Tables bei fixem Budget

In summary, the league table example and the three distinct cases above showed the following implications of the ICER threshold in a fixed budget [12]:

- **Budgethöhe bestimmt Schwellenwert bei fixem Budget**
  The most recent composition of the league table is also the currently efficient bundle of interventions. Each time a new intervention displaces an old intervention from the league table, the ICER threshold changes.
- **höhere Produktivität → niedrigere Schwellenwerte**
  Productivity (in the healthcare sector) affects the ICER threshold. Higher outcomes in the form of more QALYs (more output) with the same amount of input will decrease the ICER threshold.
- **Budgethöhe bestimmt Schwellenwert bei fixem Budget**
  The ICER threshold in a fixed budget setting is not a choice variable. The current ICER threshold depends on the financial budget. The smaller the budget, ceteris paribus, the smaller the threshold [12].
- **theoretischer Idealfall & praktische Grenzen des flexiblen Schwellenwerts im fixen Budgetsetting**
  From a mathematical perspective, the ICER threshold approach with a fixed budget and flexible ICER threshold is the "ideal case" with regard to the efficiency criterion. However, the relation between the fixed budget and flexible threshold does not exist in reality, partly because the assumptions required for this approach are not met. Therefore, no jurisdictions exist that use a league table approach, resulting in a flexible ICER threshold. For example, although the British NHS system has a fixed budget, it also has a fixed ICER threshold.

Schwellenwert aus League-Table-Ansatz berücksichtigt keine gesellschaftlichen Werte & soziale Zahlungsbereitschaft

The ICER threshold is a result from maximising health outcomes at a given time in a fixed budget setting [12]. The resulting ICER threshold is not conceptualised to consider any societal value set or WTP for an outcome. In a fixed budget setting, decisions about expanding the healthcare budget for new interventions to complement the current intervention bundle are not explicitly considered when applying theoretical principles.

A Flexible Budget Setting and a Fixed ICER Threshold

General Characteristics of a Flexible Budget Setting

vordefinierter, fixer Schwellenwert erfordert flexibles Budget

The definition and logic of the ICER threshold change when the ICER threshold is a choice variable. Once a specific ICER threshold is chosen, the budget must be flexible. From a health economic perspective, the aim in a flexible budget setting is still maximising health within a population. However, the question of whether a new intervention is efficient relates to the efficient use of additional funds to build up necessary resources for additional health outcomes. If no additional funds should be spent for a new intervention, then the situation corresponds to a fixed budget setting, which is incompatible with a fixed ICER threshold [12].

Definition of a Flexible Budget Setting

Def. flexibles Budget: zwei mögliche Budgetkonstellationen

Before the mechanism of the ICER threshold in a flexible budget setting is explained, one needs to understand the cause of how a flexible budget situation can arise in the first place. When a reimbursement decision on a new intervention is made, then two situations can arise:

- **Required budget ≤ Actual budget:** If the new intervention is cost-effective, the adoption of this technology to cover the medical needs of the target population up to the actual budget is efficient. If the new combination of health interventions completely satisfies the medical need and the required budget is smaller than the actual planned budget, some resources are "released". These additional available resources can be used for other purposes. If there is still a certain medical need because the displaced intervention had a different indication, the "released" funds or available resources could be used to cover the needs of the original displaced intervention. However, coverage can only be provided up to the amount of the remaining budget funds. Regardless of how the "released" funds are used, this situation corresponds to a fixed budget setting. Therefore, the decision rules A1, A2, B1, B3, C2, and C3 in Figure 3-1 still apply within a flexible budget setting if the funds up to the actual budget are utilised.

  erforderliches Budget ≤ tatsächliches Budget: Erstattung ist effizient, wenn Intervention kosteneffektiv

  → entspricht fixem Budgetsetting

- **Required budget > Actual budget:** In a fixed budget setting, a new intervention usually displaces an already reimbursed intervention, balancing needed and actual financial funds and resources. If a new intervention is to be reimbursed in addition to the intervention bundle already reimbursed and the actual budget is less than the required budget to finance the needed resources, the budget must be flexible upwards (budget extension).

  erforderliches Budget > tatsächliches Budget → entweder wird Budget ausgeweitet oder Annahme eines fixen Budgets

2 politökonomische Maßnahmen, um Budget auszuweiten:

Two policy options to increase the healthcare budget to fund resources for new interventions exist:

- Funds and resources could be theoretically redirected from other sectors to the healthcare sector to finance available resources for new interventions. This form of redirection has already been discussed and is represented by case 3 in a fixed budget setting above. Redirecting budget funds from other policy sectors to the healthcare system is equivalent to extending the healthcare budget. However, the redirection does not extend the jurisdiction's entire budget in the budget period, because funds are not extended only shifted.

  Mittel aus anderen Sektoren zur Finanzierung neuer Interventionen/ Ressourcen umlenkbar

- Another option to extend the budget for new interventions is issuing financial funds to fund resources if the jurisdiction has monetary sovereignty. Issuing additional financial funds is, as the decision to limit the budget, a question regarding economic policy and the institutional environment.[28]

falls geldpolitische Souveränität: Ausweitung des Budgets, um neue Interventionen/Ressourcen zu finanzieren

Both options can be observed in reality and reflect societal preferences for budgeting and economic policy in different jurisdictions.

Summary and Implications of a Flexible Budget Setting on the ICER Threshold

As outlined above, if a decision maker wants to implement a new intervention conditional on a pre-specified ICER threshold, the possibility of an upward flexible budget must be given. Additional health services require additional resources if the new intervention does not or should not displace an existing healthcare intervention. Consequently, the definition and logic of the ICER threshold change [12].

vordefinierte, fixer Schwellenwert erfordert flexibles Budget

According to Cleemput et al. [2008], the literature proposes three general approaches regarding the use of HEE and ICER thresholds in a flexible budget setting:

Cleemput et al. (2008): 3 Ansätze zum Einsatz von HEE &Schwellenwerten bei flexiblem Budget

- An alternative definition for the ICER threshold without league tables that guides healthcare decision-making,

alternative Def. von Schwellenwerten

- Application of the concept of CEA/CUA and use of the results as guidance for healthcare decision-making without a pre-specified explicit ICER threshold that is designated by law (i.e. using an implicit threshold/"rule of thumb"),

CEA/CUA als Orientierung ohne explizite Schwellenwerte

- Rejection of the ICER threshold and CEA/CUA approach but applying an alternative approach to bring economic and efficiency considerations, including opportunity cost thinking, into healthcare decision-making, e.g. by using a CBA or more recent methods in CUA [105, 106].

keine CEA, CUA & Schwellenwerte → alternative Ansätze wie CBA

Whereas the first two approaches still rely on the ICER threshold concept, the third approach completely abandons the ICER threshold concept. CBA can be categorised under the third approach. Furthermore, more recent methods in CUA try to approximate net health benefits using an estimate of the health opportunity cost of expenditure [105, 106]. Some authors also categorise cost-consequence analysis under the third approach. CCA gives an overview of the relative costs and outcomes without setting the costs and outcomes in relation to a common summarising measure (see 3.2.1 Cost-Effectiveness Analysis).

erste zwei Ansätze bauen auf ICER & Schwellenwerte

dritter Ansatz verwirft Schwellenwert-Idee

The results of a full HEE and its relation to the threshold can be represented graphically on a cost-effectiveness plane (CEP). A CEP (Figure 3-2) depicts the ICER, the uncertainty around the ICER (credibility interval) and the threshold. The CEP is the flexible budget setting equivalent to the cost-effectiveness decision rule matrix in a fixed budget setting (Figure 3-1).

Kosteneffizienz-Ebene → Äquivalent zur Entscheidungsmatrix bei flexiblem Budget

[28] Theoretically, a third option exists: Budgets within health care can be reallocated (e.g., a new fund for "innovative" medicines). This is a combination of the other two approaches. There is both a redirection (from other health care interventions/funding areas) and an expansion of budget (for a specific type of intervention/area of funding). However, it does not change the nature of the flexible budget.

If an intervention is more or equally effective and less costly (south-east quadrant including all points on the negative part of the y-axis) or if it is less or equally effective and more costly (north-west quadrant including all points on the positive part of the y-axis), the interpretation of the result is straightforward. The former result indicates that the new intervention is cost-effective, and an adoption is recommended, while in the latter, the new intervention is not cost-effective compared to an alternative and should not be adopted. Both decision rules correspond to situations A1, A2, B1 (south-east quadrant) and B3, C2, C3 (north-west quadrant) in a fixed budget setting (Figure 3-1).

Südost-Quadrant = kosteneffektiv → erstatten

Nordwest-Quadrant = nicht kosteneffektiv → nicht erstatten

entspricht A1/A2/B1 & B3/C2/C3 in Entscheidungsmatrix (fixes Budget)

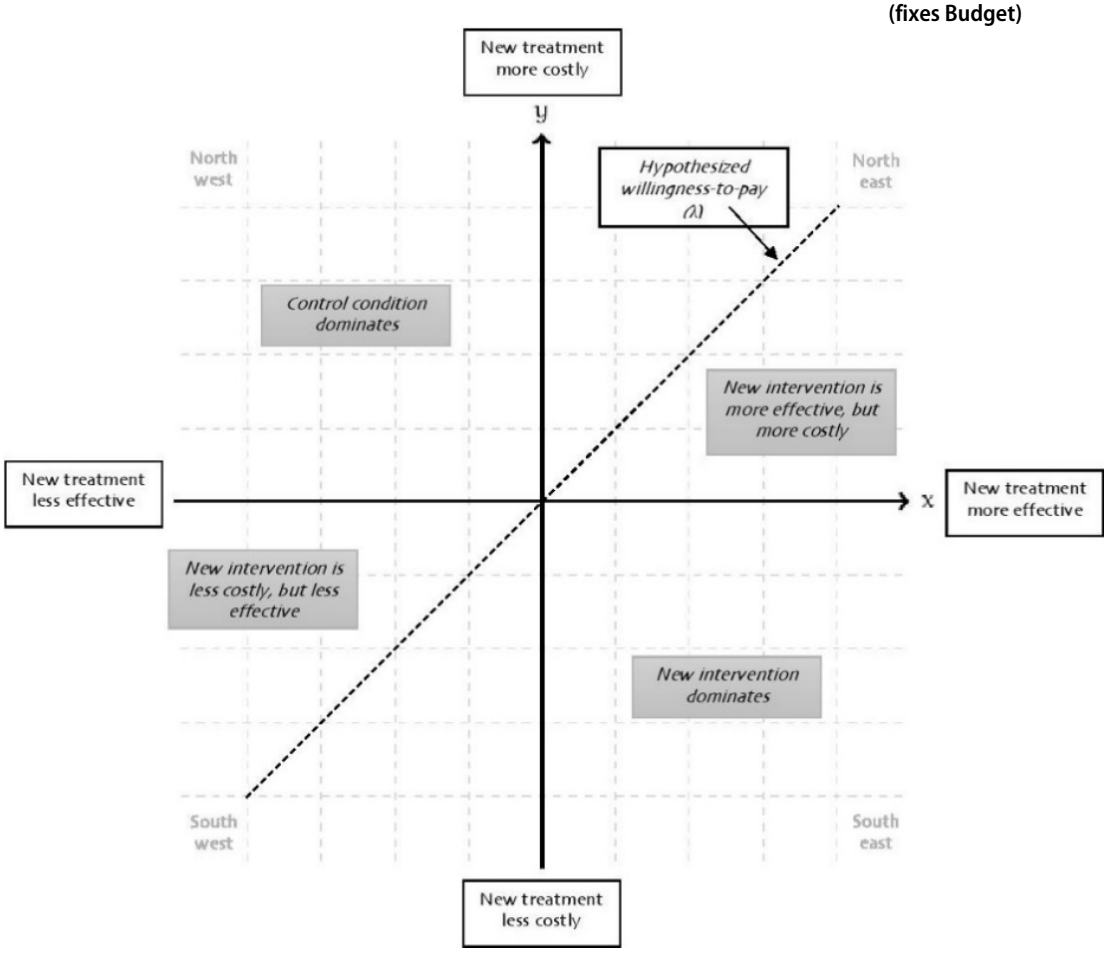


Figure 3-2: Cost-effectiveness plane (CEP) taken from Zechmeister-Koss et al. [2019] with permission of the authors

In most cases of evaluations of newly marketed interventions, the intervention is both more effective and more expensive [11, 15]. This situation corresponds to the northeast quadrant. In this situation, decision makers must choose whether additional funds should be spent for additional health effects, and the ICER threshold comes into play. The dashed line represents a hypothesised ICER threshold in Figure 3-2.

Nordost-Quadrant: effektiver, aber teurer → Schwellenwert entscheidet, ob zusätzliche Mittel ausgegeben werden

Technologies with an ICER below the proposed ICER threshold indicate that the health gains are worth the additional funds spent on the new intervention. If the ICER lies above the ICER threshold, the additional health outcomes are not "worth" the additional funds, and the new intervention should not be reimbursed.

ICER ≤ Schwellenwert: zusätzliche „Gesundheit" rechtfertigt zusätzliche Mittel

The following implications of the ICER threshold in a flexible budget apply [12]:

Implikationen eines flexiblen Budgetsettings:

- The ICER threshold in a flexible budget setting can be a choice variable. The needed resources (budget) depend on the fixed ICER threshold.

fixer Schwellenwert → flexibles Budget

- The question of whether a new intervention is efficient relates to the efficient use of additional funds to build up necessary resources for additional health outcomes. Additional funds can be brought up by redirecting them from other policy domains or issuing financial funds if the jurisdiction has monetary sovereignty. Issuing additional financial funds is a question related to economic policy.

2 politökonomische Maßnahmen, um Budget auszuweiten

- If no additional funds should be spent for a new intervention, then the situation corresponds to a fixed budget setting, which is incompatible with a fixed ICER threshold.

keine zusätzlichen Mittel → unvereinbar mit fixem Schwellenwert (entspricht festem Budgetsetting)

In summary, if the ICER threshold is an exogenously fixed value, a flexible financial budget to fund necessary resources would be required. If the budget and resources are fixed, the ICER threshold results from maximising health outcomes and is no choice variable. These assertions are not arbitrary. The relationship between the budget type and the nature of the ICER thresholds results from the HEE's logic.

fixer Schwellenwert erfordert flexibles Budget & fixes Budget erfordert flexiblen Schwellenwert

3.3.4 ICER Threshold Methods and Fixed versus Flexible Budget Constraints

Health economists use different methods to derive thresholds [8]. In the literature, one way to categorise the different approaches is to distinguish between supply-side or demand-side thresholds [9, 11, 101, 107-109].

angebots- & nachfrageseitige Schwellenwerte

- Supply-side interpretation or k-thresholds (correspond to a fixed budget setting): The ICER threshold reflects the opportunity costs in a fixed budget setting – the value of a health gain foregone from the next best use of the resources involved in adopting a cost-increasing technology [11, 109]. The supply-side approach is based on the marginal productivity of healthcare spending. The theoretical application was demonstrated within the league table approach. However, as mentioned, the league-table approach is rarely used because decision or policy makers rarely have information on the cost per QALY for all potential interventions [100]. Therefore, other approaches to approximate k-thresholds exist, which are described below in Section 3.4.1 on Empirical ICER Thresholds in a Fixed Budget Setting: Opportunity Cost Threshold Approach. If certain assumptions are fulfilled, the values from the alternative approaches correspond to the threshold from the league table approach or at least are an approximation of it [11].

angebotsseitige Interpretation: Schwellenwert = Opp.-Kosten in einem fixen Budget-Setting basierend auf marginaler Produktivität der Gesundheitsausgaben

verschiedene Ansätze zur Schätzung existieren

- Demand-side interpretation or v-thresholds (corresponds to a flexible budget setting): The ICER reflects the additional societal WTP for an additional health outcome or the opportunity cost based on additional spending in a flexible budget setting [11, 109, 110]. Methods to elicit societal WTP by employing questionnaires are listed in Section 3.4.3 Universal ICER Thresholds and Societal Willingness to Pay ICER Thresholds (Societal WTP Thresholds).

nachfrageseitige Interpretation: Schwellenwert = Opp.-Kosten in einem flexiblen Budget-Setting basierend auf zusätzlicher Zahlungsbereitschaft

Unterschied zwischen angebots- & nachfrageseitigen Schwellenwerten umstritten

The distinction between supply-side and demand-side thresholds can be contested for several reasons. Within a fixed budget setting, a k-threshold based on past reimbursement decisions (known as a supply-side threshold) can be reinterpreted as a demand-side threshold. While estimated supply-side thresholds are based on the marginal productivity of healthcare spending and show what health gains the system must give up, they can be understood as reflecting "revealed" societal preferences through budget allocations by decision or policy makers [11]. This reinterpretation works because budget decisions themselves reflect societal choices – the political process[29] of setting healthcare budgets reveals collective preferences about healthcare spending. In essence, budget constraints embody collective choices about healthcare resources, making the supply-side threshold an implicit expression of societal WTP.

in der Praxis: Abweichung von angebots- & nachfrageseitigen Schwellenwerten

However, in practice, k-thresholds may differ from demand-side thresholds (v-thresholds), reflecting the different methods of preference elicitation. The differences can be quite significant. The social value (societal WTP) of a QALY in the NHS is £ 70,000 per QALY (v-threshold), thus substantially exceeding the estimated marginal productivity of healthcare spending of £ 15,000 per QALY (k-threshold) by the Department of Health and Social Care (DHSC) [112]. This observation indicates that under a fixed budget a new health care intervention would only be implemented if the ICER would be smaller than £ 15,000. Any amount above would mean that the fixed budget would need to be expanded.

Auswirkungen eines flexiblen Budgets bei angebotsseitigen Schwellenwerten

Furthermore, the supply-side approach is also relevant, where the budget is flexible. If the budget can be extended to fund a new intervention, then the decision-maker would want to know what could be achieved with alternative uses of those additional resources if spent on other currently-not-funded healthcare interventions.

Schwellenwert reflektiert Opp.-Kosten bei neuem Budget, ist höher als unter vorherigem Budget & geringere Verdrängungseffekte

The threshold then …

- Reflects the opportunity cost at the new budget level.
- Is likely to be higher than under the initial, fixed budget.
- Represents marginal benefit (productivity) of additional spending.
- Requires potentially less displacement of existing services.

auch institutionelle Faktoren bestimmen Schwellenwert …

This demonstrates that thresholds are not fixed technical parameters but depend on institutional and budgetary contexts, explaining why healthcare systems with different budget arrangements might employ different thresholds.

… aber Budgettyp hat eine zentrale Rolle für die Schwellenwert-Logik

Therefore, we argue that a distinction regarding the budget setting is more appropriate than a demand- and supply-side distinction, as the method and logic of the threshold significantly depend on the budget type. That does not mean that the ICER thresholds are solely determined by the budget type, as mentioned above (see Section 3.3 on Incremental Cost-Effectiveness Ratio and Thresholds) [99].

[29] The specific method of forming or incorporating societal preferences – whether through consultative methods, democratic elections, or authoritarian responsiveness – is not relevant to this discussion [111].

3.4 Methods to Specify ICER Thresholds

Commonly used methods to specify ICER thresholds exist:

Übersicht verschiedener Schwellenwert-Methoden:

- Empirical ICER thresholds[30]
  - Empirical ICER thresholds in a fixed budget setting: Opportunity cost threshold approaches including the league table approach ("Supply-side thresholds" or k-thresholds)
  - Empirical ICER thresholds in a flexible budget setting

empirische Schwellenwerte im fixen & flexiblen Budgetsetting

- Gross domestic product-based (GDP) or value of a statistical life ICER thresholds

BIP-basierte

- A universal ICER threshold and societal willingness to pay ICER thresholds (societal WTP thresholds)

gesellschaftliche Zahlungsbereitschaft

- Efficiency frontier or benchmark approach

Effizienzgrenzen-Ansatz

3.4.1 Empirical ICER Thresholds

General Characteristics of the Empirical ICER Thresholds

Within the empirical ICER threshold approaches, one must distinguish between empirical ICER thresholds within a fixed and flexible budget setting. Regardless of the budget setting, both empirical ICER threshold approaches use cost-effectiveness data from past reimbursement decisions or historical expenditure and outcome data to calculate a threshold. [9, 108].

empirische Schwellenwerte basieren auf vergangenen Erstattungsentscheidungen

Empirical ICER Thresholds in a Fixed Budget Setting: Opportunity Cost Threshold Approach

In the literature, empirical ICER threshold approaches in a fixed budget setting are labelled as "true" opportunity cost approaches [11, 98]. One of the related opportunity cost threshold approaches that have already been discussed is the league table approach. However, four other interrelated empirical ICER threshold approaches exist. All these concepts have in common that they are embedded in a fixed budget setting. A new efficient situation is established only if the least cost-effective programme is displaced.

4 verschiedene empirische Ansätze zur Opp.-Kostenbestimmung:

The four opportunity cost threshold approaches are extensively discussed in Sampson et al. [2022]:

- **Shadow price of health:** The threshold represents the cost per unit of health gain. The shadow price is calculated by league tables, programme budgeting, or marginal analysis (i.e., the analysis of a small amount of additional input resources/expenditures on the output such as HLY). The required data and evidence requirements comprise cost-effectiveness data of all current and potential expenditure programmes, accounting for budget impact and the timing of expenditures.

„Shadow Preis" der Gesundheit → Kosten pro marginalem Gesundheitszuwachs

stellt hohe Datenanforderungen

[30] In principle, all threshold approaches are empirical. However, only historical data on reimbursement decisions is used to calculate the thresholds within the empirical ICER threshold approach. Another term would be historical ICER thresholds.

- **The marginal product of health:** The threshold represents the change in health (output) per unit change in expenditure (inputs) "at the margin", i.e. the marginal product of health, which is the value of the last output that corresponds to a small amount of additional input resource spent. Linear programming and estimation of coefficients of a production function (regression or stochastic frontier analysis) are used for this type of opportunity cost. For this approach to work, data on health spending, capital, and labour (inputs) and mortality or QALY data (output) for different intervention programmes or individual patients at different sites and times are required. The variation across observations needs to be exogenous, i.e. the random part or the part that the model cannot explain must be independent and individually distributed.

Berechnung des Gesundheitsgrenzprodukts durch verschiedene (ökonometrische) Schätzmethoden oder Input-Output-Analyse

- **Average displacement of health:** The threshold represents the average change in health outcomes per average change in expenditures under observed budget contractions or expansions. New cost-effective technologies relative to this threshold would improve the efficiency of health care expenditure on average. For this approach, the same data requirements apply as in the marginal product of the health approach. However, the observations do not need to be exogenous. To get valid estimates and to control for the endogeneity of health care spending, the application of experimental or quasi-experimental (causal inference methods) with instrumental and control variables is required.

Schätzung der durchschnittlichen „Gesundheitsverdrängung " durch kausale Analysemethoden

- **Outcome elasticity:** The threshold represents the optimal percentage change in health per 1% change in expenditure (average proportional relation between budget changes and health output). Evidence requirements correspond to the average displacement approach, and data sources correspond to the marginal product approach. The outcome elasticity is estimated by linear regression of health outcomes on health spending or by log-transformations of these variables.

Outcome-Elastizität & prozentuale Gesundheitseffekte durch Regressionsanalyse

One of the most influential attempts to estimate an empirical ICER threshold approximating "true" opportunity cost in the sense of average displacement of health (third approach above) is an econometric analysis by a research group around Claxton et al. [2015]. In a 2-year project funded by the National Institute for Health Research (NIHR), the authors developed a complex approach to estimate a National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold using routinely available data. The authors used programme budgeting (PB) data on 23 programme budgeting categories (PBCs) and displacement decisions taken across the NHS[31].

UK Studie zur Berechnung eines Schwellenwertes anhand von NHS-Daten

→ Schätzung der durchschnittlichen „Gesundheitsverdrängung"

The authors conducted a three-stage econometric analysis using the PB expenditure data from the year 2008 to estimate an overall cost per QALY threshold:

3-stufiger ökonometrischer Ansatz:

- First, the authors translated estimated effects on mortality into life-years, considering the "counterfactual" deaths that would have occurred

von Mortalitätsdaten zu QALYs

[31] The PB data was expenditure data by Primary Care Trusts (PCTs). PCTs were local administrative healthcare bodies responsible for commissioning health care services. The PB data allowed the PCTs to examine the health gain obtainable through investment and identify potential shifts in investment to optimise local health gains, reduce health inequalities and improve value for money [113]. Programme budgeting seeks to allocate all types of PCTs expenditure to the various PBCs, including secondary care, community care and prescribing [98].

if the population in a given PBC faced the same mortality risks as the general population. However, not all 23 PBCs have a mortality effect.

- In the second step, the authors adjusted the life-year effects of a particular disease by gender and age at which the life-years are gained or lost. This step ensures that the life-years estimated in step one reflect the age-, gender-, and disease-specific QoL component resulting from changes in expenditure.
- In the final step, they incorporated the "pure" QoL effects, i.e., effects on health that are not directly associated with mortality and life-year effects.

empirischer & „offizieller" NICE-Schwellenwert zeigen große Diskrepanz

Claxton et al. [2015] estimated an inflation-adjusted threshold of £ 12,936 per QALY, which is far below the current applied fixed threshold range of £ 20,000 to 30,000.

Verteilung der NHS-Gesundheitseffekte:

mortalitätsrelevante Programme dominieren Gesamtwirkung & Ausgabeneffizienz

The 23 different programme budget categories have different impacts on the health effects given the change in expenditures. Eleven of the 23 PBCs account for 50% of the total expenditures and 78% of the overall health effects. These eleven PBCs are also the disease categories with mortality effects that could be estimated. They focus on infectious diseases, cancer, endocrine, nutritional and metabolic problems, neurological problems, circulatory problems, respiratory problems, gastrointestinal problems, genitourinary problems, maternity and neonates, and the residual programme, where about two-thirds of expenditures are attributable to primary care. The other 12 PBCs only account for 22% of the overall health effects, meaning they have a higher cost per QALY as the associated marginal expenditures lead to smaller health increases. The 12 PBCs are disorders of blood, mental health disorders, problems of learning disability, problems of vision, problems of hearing, dental problems, problems of the skin, problems of the musculoskeletal system, problems due to trauma and injuries, adverse effects and poisoning, healthy individuals, and social care need.

Schlussfolgerung: zu hoher NICE-Schwellenwert & negative Auswirkungen auf NHS-Gesundheitseffekte

Uncertainty analysis showed that the probability the threshold is smaller than £ 20,000 per QALY is 0.89, and the probability that it is smaller than £ 30,000 per QALY is 0.97. The authors conclude that considering structural uncertainty, the estimate of £ 12,936 per QALY is, on balance, the best estimate or even likely to be an overestimate, because this number results from actual reimbursement data. Overall, the results indicate that the threshold range NICE currently applies leads to new interventions being more likely to be reimbursed and displacing health gains elsewhere in the NHS [98].

Claxton-Methodik: Indirekte QALY-Berechnung & Abgrenzung zu anderen empirischen Ansätzen

What is apparent in this approach is that the authors used real-world mortality and life-year effects to approximate QALYs indirectly. The authors did not use directly elicited QALY changes from publications previously considered in reimbursement decisions. While other studies in this domain estimated elasticities between expenditures and outcomes [114] or estimated marginal productivity [109, 115-117], this approach corresponds to the concept of average displacement of health. Furthermore, this concept must be distinguished from empirical ICER thresholds that are used for future reimbursement decisions within a flexible budget setting.

Kritik an empirischen Schwellenwert-Methoden: Datenqualität & kausale Beziehungen als Schlüsselfaktoren

The publication by Sampson et al. [2022], which was funded by an unconditional grant from the Association of the British Pharmaceutical Industry (ABPI), states that only the shadow price concept accurately estimates opportunity cost, while the other three including the average displacement of health approach only provide imperfect estimates[32]. The shadow price approach also has the highest evidence requirements and requires data on the HEE of all individual interventions funded and unfunded. When using one of these approaches, it is obligatory to have knowledge of the causal relation between cost and outcome data. Otherwise, the estimates may not be valid due to reverse causality [11]. Furthermore, the possibility of estimating an ICER threshold by these approaches stands and falls with the expenditure and outcome data quality. Outcome data, such as life expectancy, and expenditure data are related. Highly aggregated data, in turn, bear the risk of heterogeneity and lack of control for individuals' health care needs [11].

Methodenstreit über Schwellenwert-Methode

A letter to the editor by Claxton et al. [2024] countered the argument made by Sampson et al. [2022] that only the shadow price approach gives an accurate estimate of opportunity cost. Claxton et al. [2024] argue that their and similar attempts give the best estimate of the expected health effects of exogenous changes in available health care expenditure [98, 116, 119].

Diskrepanz zwischen empirischer Berechnung & praktischer Anwendung von Schwellenwerten im fixen Budgetsetting

The actual application of the empirically derived thresholds by jurisdictions is different in practice. Once an empirical threshold is estimated based on past reimbursement decisions, the estimated threshold becomes fixed and used in a flexible budget manner in future reimbursement decisions.

Empirical ICER Thresholds in a Flexible Budget Setting

empirischer Ansatz im flexiblen Budgetsetting:

Verknüpfung von Gesundheitsausgaben & politischen Zielen hinsichtlich der Lebenserwartung

One approach that can be categorised under the empirical ICER threshold approach in a flexible budget setting can be found in the publication by Pichon-Riviere et al. [2023]. They estimated cost-effectiveness thresholds based on health expenditures per capita and life expectancy data for 174 countries. The authors developed a conceptual framework to assess how the adoption and coverage of new interventions with a given incremental cost-effectiveness ratio will affect the rate of increase of health expenditures per capita and life expectancy at the population level. The novelty of this approach is that the cost-effectiveness threshold is calculated in such a way that it considers predefined policy goals regarding the evolution of life expectancy and health expenditure per capita (flexible budget setting).

Ansatz ist eine Alternative zur klassischen Schwellenwertbestimmung

Pichon-Riviere et al. [2023] propose their approach as an alternative to "classical" empirical approaches that require the knowledge of a lot of information regarding past reimbursement decisions such as past evaluation methodologies, information on technologies, costs, expenditures, and previously relevant comparators, which may not be available. To arrive at a country-specific threshold within this approach, the political decision maker in charge of the threshold would only specify the path of health spending and life expectancy increases in which they expect to remain in a given period [9]. The threshold value is then calculated based on these two variables.

Pichon-Riviere et al. (2023): Schwellenwerte meist unter 1x BIP pro Kopf

The results in Pichon-Riviere et al. [2023] show cost-effectiveness thresholds per QALY of less than 1 x GDP in 97% of the 174 countries analysed. Furthermore, the authors mention several unique characteristics of their approach:

[32] The extent to which the presentation of results in Sampson et al. [2022] were influenced by the ABPI funding is unclear.

Besonderheiten der Methode:

Makrodatennutzung & Anwendungsflexibilität auf verschiedenen Ebenen

- The estimated thresholds are based on generally available macro-level data, can be easily updated, and the two underlying concepts, life expectancy and health care expenditures are easy to understand.
- The concept incorporates the direct relationship between the threshold and health care budget: An increase in the health care budget, and consequently, the annual rate of increase in health expenditure, increases the estimated threshold.
- The estimation of cost-effectiveness thresholds is based on per-capita expenditure on health, not GDP: Differences in the productivity of health spending among countries with a similar GDP become more apparent.
- The approach can be applied to subnational levels or subsectors within a single country, enabling the estimation of different thresholds.
- The approach is based on current health system efficiency and efficiency trends.

Ansatz hat aber auch Limitationen

bspw. unklare Kausalität zwischen Gesundheitsausgaben & Lebenserwartung

Although the approach builds on few but strict assumptions, the approach has still a few drawbacks. One of the main assumptions (that observed changes in life expectancy are due solely to changes in health expenditure) can be challenged [120], important explanatory variables that explain both life expectancy and expenditure are neglected. There is also a risk of reverse causality, as health expenditure cannot only influence life expectancy but vice versa: an increase in life expectancy can also influence expenditure. Nevertheless, the approach may be an option for countries that do not have a threshold so far to calculate some form of opportunity cost.

Grenzen der Interpretation empirischer Schwellenwerte als gesellschaftliche Zahlungsbereitschaft

Some scholars interpret the empirical ICER threshold in a flexible budget setting as a societal WTP threshold [8, 9]. The argument is that if a decision maker reimbursed an intervention in accordance with the ICER threshold applicable at that time, any new intervention that is efficient is socially accepted. However, as will be described in the proceeding subsection on societal WTP thresholds, more sophisticated methods are required to derive a societal threshold that truly reflects societal preferences and values.

Validität empirischer Schwellenwerte teilweise durch nicht-effizienzbezogene Faktoren in Erstattungsentscheidungen begrenzt

Furthermore, whether reimbursement decisions in the past were solely based on efficiency aspects is also questionable [8, 12]. This has an impact on the reimbursement and expenditure data. It may also become apparent that the decisions made in the past were not optimal from the current standpoint because thresholds in the past were too high [12]. There is evidence that for some medicines in cancer care and for orphan diseases [121, 122], criteria other than efficiency were decision-relevant [8, 123]. This observation, in turn, impacts the validity of most empirical ICER threshold approaches in the first place if no information on the consideration of efficiency aspects is available and no valid outcome measures are set in relation to costs or expenditures.

Transparenz & Vollständigkeit historischer Daten als Voraussetzung für empirische Schwellenwerte

Therefore, for this approach to work, transparency on (positive and negative) funding decisions, additional decision-relevant aspects, and the explicit role of HEE in previous decisions must be available. This also includes complete information on the past evaluation methodologies, whether they are comparable, and information on existing technologies, costs, expenditures, and previously relevant comparators. In reality, such conditions are not constant and consistent over time [8, 12].

3.4.2 GDP-Based ICER Thresholds

BIP-basierte Schwellenwerte:

BIP pro Kopf als Maßstab für „Wert" der Gesundheit & Einkommensverluste

ICER thresholds based on a country's per-capita gross domestic product (GDP) or national income are the most commonly cited thresholds [123, 124]. The reason for using the GDP-based threshold is that GDP is a proxy for earnings or available income. Ill health has a negative impact on these earnings and affects also the GDP. The averted DALY by the expenditures for an intervention offsets the loss of income, keeps the person in the labour market, and potentially creates an additional return on investment by fiscal multiplier effects on the GDP [107]. Furthermore, earnings reflect the value of leisure time in addition to market consumption, which can be interpreted as a form of WTP for an additional unit of health [125].

Ursprung BIP-basierter Schwellenwerte in WHO-CHOICE-Projekt

The GDP per capita approach was initially developed within the World Health Organization's (WHO) project "Choosing Interventions that are Cost-Effective (WHO-CHOICE)" [126]. The initially proposed GDP-based threshold reflects the estimated economic value of a year of healthy life in terms of income using DALYs.

Schwellenwerte: Einfaches & dreifaches BIP pro Kopf pro verlorenes gesundes Lebensjahr (DALY)

According to this approach, an intervention is …

- cost-effective if the cost per DALY avoided is less than three times the national GDP per capita, and (Cost in monetary unit/DALY ≤ 3 x GDP of a country)
- very cost-effective if the cost per DALY avoided is less than one times the national GDP per capita [9, 126] (Cost in monetary unit/DALY ≤ 1 x GDP of a country)

WHO kritisierte ursprünglich inkrementelle CEA/CUA & bevorzugte generalisierte CEA für Interventionsmix & Ressourcenallokation

The WHO does not specifically criticise other ICER threshold methods but argues that the HEE studies currently used elsewhere add single interventions one at a time (incremental analyses), which may not result in the optimal use of resources. The WHO argues that CEA or CUA are not designed to assess the current mix of interventions, are setting-specific, and are based on incremental CE information with inconsistent methodologies [127]. On the contrary, according to the WHO, the generalised cost-effectiveness analyses (GCEA) are more general about assessing different interventions' costs and health benefits. Various highly variable context-specific decision constraints are not considered. The only remaining factor is the availability of resources when using a generalised league table for priority setting [127]. The GDP-based ICER threshold informs policy makers how to plan and organise their health system from a long-term perspective. In addition, the approach should give information on what could be achieved if decision makers could start to build the health system again, i.e. redistribute all healthcare resources [127].

WHO: Ansatz berücksichtigt Freizeit, Konsum, Lebensqualität & -erwartung

The WHO tried to account for leisure time, non-health consumption, longevity, and HRQoL in the calculation of this threshold by accounting for these aspects in the denominator of the threshold, e.g., by using a value of a statistical life (VSL) as an outcome [127].

auch Kritik an WHO-Ansatz: erfasst Dimensionen wie Freizeit & Lebensqualität nicht adäquat …

Although the WHO Commission initially suggested that jurisdictions should generally use these values, the thresholds were only used as a rule of thumb, mostly in Low and Middle-Income Countries (LMICs) and are still used in some Eastern European countries (see Chapter 4.1) [107]. Even though the WHO approach tried to capture additional dimensions such as leisure time or HRQoL, the method has been criticised because it does not adequately capture these additional dimensions. Even the WHO acknowledges the limit-

tions [124, 128]. Critics argue that "people also value dimensions beyond income". Additionally, a country's specific budget, technical capacity, preferences on WTP or other societal values are not properly taken into account by this approach. Another strand of criticism pertains to the concept itself. The approach resembles the value of a statistical life (VSL), placing a monetary value on life, which comes with ethical problems and potentially leads to incommensurable situations.

… zudem: länderspezifische Faktoren (Budget, Präferenzen etc.) werden nicht berücksichtigt

teils auch ethisch problematisch

Critics argue that the WHO's GDP-based ICER thresholds are higher compared to ICER thresholds elicited by other methods [9]. Consequently, a positive reimbursement or implementation decision is highly likely [123]. The relatively high threshold level and the high probability of a positive reimbursement decision may result from the WHO's evaluation approach – the GCEA. According to the WHO's "Guidelines on generalized cost-effectiveness analysis", the evaluation of an intervention's cost-effectiveness is "comparing against the null" (natural history of disease) [12, 127]. Different countries may already have different care standards in different healthcare domains, and "doing nothing" does not reflect the current SOC [124]. Comparing a new intervention with "doing nothing" clearly results in a higher incremental effectiveness and, consequently, a higher denominator than comparing it to an already established SOC. The higher the denominator of an intervention's ICER, the lower the ICER, making the ICER threshold easier to meet.

WHOs BIP-basierter Schwellenwert höher als andere Methoden → begünstigt positive Erstattungsentscheidungen

However, the argument by the WHO that CEA or CUA are not designed to assess the current mix of interventions is also not completely accurate. CEA or CUA may currently not be applied to assess the current mix of interventions, but it is possible [129].

CEA/CUA können durchaus für Bewertung des aktuellen Interventionsmix angewandt werden

3.4.3 Universal ICER Thresholds and Societal Willingness to Pay ICER Thresholds (Societal WTP Thresholds)

The idea behind the societal WTP thresholds method is that the resulting threshold reflects the societal preferences and values of the relevant population groups in relation to health gains [8, 100, 108]. The societal WTP for an additional health gain, such as QALY, is the amount of budget funds or resources society is temporarily willing to give up from somewhere else to obtain the additional health gain. The temporarily given funds or "borrowed" resources can originate from funds intended for other interventions in other disease classes or other policy domains [12].

gesellschaftliche Zahlungsbereitschaft (WTP) = Betrag aus Budget/Ressourcen, den Gesellschaft für zusätzliche Gesundheit umverteilen möchte

If the societal WTP threshold is related to QALYs, the following three steps are carried out to calculate a universal societal WTP threshold from individual preferences:

3-stufiger Prozess zur Kalkulation von WTP

- **Eliciting QALYs for different health states:** In the first step, it is necessary to calculate the utility difference between two health states (e.g. "healthy" and status quo) by time trade-off, standard gamble, or visual analogue scale [8]. It is assumed that newly funded interventions establish a healthy state, and that the status quo is "doing nothing" or the current gold standard.

Ermittlung von QALYs

- **Eliciting WTP for the health gains due to a new intervention:** In the next step, either a revealed preference approach (wage risk) or a stated preference approach (contingent valuation) is used to elicit the monetary value a patient is willing to pay for the health benefits (i.e. the increased QALYs).

Ermittlung der Zahlungsbereitschaft für QALYs der neuen Intervention

- **The ratio between WTP and QALY differences:** In the final step, the resulting monetary value and the health benefit are set in a ratio to obtain the societal WTP threshold.

Verhältnis zwischen Zahlungsbereitschaft & QALY-Differenz

However, estimating a universal societal WTP threshold for a health gain from individual preferences without considering societal preferences across all disease classes or different populations can be methodologically problematic. The aggregation of individual preferences into a joint WTP threshold that should reflect societal preferences on different diseases or populations leads to an abstraction of the individual person's characteristics, such as health status, socio-economic characteristics, and demographic aspects [12].

aber auch methodische Probleme bei Ableitung universeller Zahlungsbereitschaften (bspw. Aggregation individueller Präferenzen)

Decision and policy makers in some jurisdictions implicitly already consider societal preferences when making reimbursement decisions. If societal preferences are reflected in the threshold and in addition in the decision-making process, this leads to double counting.

Entscheidungsträger berücksichtigen Präferenzen bereits implizit

For these reasons, one solution is to explicitly consider societal preferences and values to define different ICER thresholds (see Chapter 3.5). The weighting of QALYs allows the incorporation of socially relevant aspects, such as equity considerations and aspects beyond the mere valuation of health. For example, by giving weights to health outcomes according to specific population groups, QALYs of one population group can be valued higher than other population groups. The weights can be chosen according to societal preferences on specific health-related topics or to specific characteristics society deems decision-relevant [12]. Topics and decision-relevant characteristics comprise the severity of the disease (disease burden, disease category, end-of-life related), rarity of the disease and availability of treatment alternatives (orphan disease), distribution of health risk, equality of healthcare access or general distributional aspects (income distribution). The incorporation of weights would result in different societal WTP thresholds conditional on different societal aspects or at least an adjustment of the baseline societal WTP threshold.

zusätzliche Gewichtung von QALYs ermöglicht Einbeziehung von Equity & sozialen Aspekten über reine Gesundheitsaspekte hinaus

Cleemput et al. [2008] show that by considering societal preferences, the threshold for interventions that reduce the mortality risk could be higher than for interventions that improve QoL. The societal WTP threshold method would even allow the societal WTP threshold to be ad-hoc reassessed depending on the intervention. This approach would require the budget to be more flexible and undermines the intended idea of a single fixed ICER threshold [12]. However, eliciting all relevant societal preferences on aspects such as income distribution or distribution of health risks to calculate health outcome weights is labour-intensive and not straightforward. Therefore, studies calculating thresholds using weights dependent on societal preferences are very rare.

Berücksichtigung gesellschaftlicher Präferenzen → höhere Schwellenwerte für mortalitätsreduzierende im Vergleich zu lebensqualitäts-verbessernde Interventionen

In summary, the societal WTP threshold results heavily depend on the approach used. The methods "revealed or stated preferences", introduced in sections 3.2.2 and 3.2.3 for deriving QALYs and assigning monetary values to the costs and benefits of interventions, can also be used to derive societal WTP thresholds. However, revealed or stated preference approaches for calculating societal WTP thresholds exhibit the same bias potential as outlined earlier.

Verzerrungspotenziale wie bei QALY-Bewertung

3.4.4 Efficiency Frontier Approach (Benchmark Approach)

Effizienzgrenzen-Ansatz (EFA) setzt Preisobergrenze → kein ICER-Schwellenwert

One approach that does not rely on an explicit ICER threshold but provides a price ceiling for new interventions is the efficiency frontier approach (EFA). The IQWiG in Germany used this approach until the end of 2023, and it is still used in Belgium by the KCE and in France by the HAS [10, 12, 130-132].

effizienteste Kombination verfügbarer Interventionen bildet Effizienzgrenze

The most efficient combination of currently available interventions forms the efficiency frontier within the EFA. If a new intervention comes to the market, the ICER of the new intervention is embedded within this efficiency frontier. A potential price ceiling is calculated by using the proportional rule. This decision rule can be applied in three ways [133]:

Basisfall: ICER der neuen Intervention ≤ ICER nächst effektiver Alternative

- **Base case:** The ICER of a new intervention should not be higher than the ICER of the next effective intervention compared with its next effective intervention (i.e. the comparator's comparator). This implies that the incremental costs of a new intervention may only increase in proportion to the incremental effects for the new intervention to be reimbursed (base case rule).

Variante 1: ICER der neuen Intervention ≤ ICER effektivster Alternative vs. keine Intervention

- **Stricter variation 1:** The ICER of a new intervention should not be higher than the ICER of the currently most effective intervention compared with no intervention (no intervention rule).

Variante 2: ICER der neuen Intervention ≤ Durchschnitts-ICER aller nicht-dominierten Alternativen

- **Stricter variation 2:** The ICER of a new intervention should not be higher than the ICER of the average ICER of all non-dominated alternatives (average ICER of non-dominated alternatives rule).

Varianten 1 & 2 führen zu niedrigeren Preisobergrenzen

The stricter versions of the proportional rule lead to lower ceiling prices [133]. Comparing against the null (natural history of disease) leads to greater health increases than a comparison against the next effective intervention, which makes the denominator larger and, hence, the whole value smaller. In Germany, if the price of a drug was above the ceiling price, patients had to pay the difference out of pocket [133]. The stricter variation 1 of the EFA also considers disease severity. The health gain of comparison with no intervention is larger in most cases than the health gain using an adequate comparator. Hence, in that case, the degree of consideration of disease severity is also small. It is assumed that the disease is more severe if there is no comparison intervention or no comparison with any intervention [133].

Variante 1 berücksichtigt auch Krankheitsschwere

EFA in Deutschland (bis 2023) fokussierte auf effiziente Interventionen innerhalb eines spezifischen Therapiegebiets

Although the German healthcare system goals only vaguely describe the efficient handling of resources, applying the EFA before 2023 followed specific context-dependent characteristics. For example, although comparators of a medicinal product could have been any health intervention, the efficiency frontier consisted of the most efficient combination of currently available interventions in a specific therapeutic area. The focus on a specific therapeutic area is at odds with textbook health economics, which recommends that efficient use of resources be analysed across the entire healthcare system [134]. At present, in HTA reports with economic evaluations by the IQWiG (e.g. ThemenCheck Medizin), societal values and setting priorities across the healthcare system are not directly accounted for in the HEE. However, these issues may be addressed in separate ethical analyses and may be incorporated in the deliberative process of reimbursement decisions by decision makers [10].

The EFA to derive a ceiling price can be used in a fixed- and flexible budget setting. IQWiG's EFA was embedded in a flexible budget setting with the assumption of infinite resources. The needed resources are only constrained by the potential health improvements due to the proportional rule. If the EFA is undertaken in a fixed budget setting, the same rules apply as within the league table approach in a fixed budget setting. The decisive ICER is defined by the last cost-effective, still financed intervention in the league table before the budget is exhausted. If a new intervention has a higher ICER than this decisive ICER, the ceiling price for the new intervention must equal to this value. Hence, the decisive ICER and derived ceiling prices must be constantly readjusted in a fixed budget setting [133].

EFA kann bei fixem und flexiblem Budget angewendet

EFA in Deutschland ging von unbegrenzten Ressourcen aus (flexibles Budget)

3.4.5 Overview of ICER Threshold Methods

Table 3-13 summarises the presented approaches to derive an ICER threshold.

Übersicht der Methoden in Tabelle 3-13

Table 3-13: Overview of approaches to derive an ICER threshold

Approach	Description	Single ICER threshold
Empirical ICER threshold in a fixed budget setting: Opportunity cost approach	Shadow price, the marginal product of health, the average displacement of health, and outcome elasticity approaches are used to derive opportunity cost based on the question of whether the improvement in benefits that the new technology offers exceeds the improvement that would have been possible if the additional resources required had, instead, been made available for other health care activities. This assessment is required whether the additional costs of the technology would be accommodated from existing commitments or whether additional health care resources would be made available to fund them	In principle no, but a single ICER threshold to reflect health opportunity cost can be estimated to serve as a pragmatic approximation to an otherwise intractable optimisation problem
Empirical ICER threshold in a flexible budget setting	An empirical threshold is estimated using cost-effectiveness data of interventions previously approved for reimbursement or expenditure and outcome data. The threshold is fixed and universally applied in future reimbursement decisions and used in a flexible budget setting.	Single or multiple baseline ICER thresholds possible (if calculated and applied for each illness class)
GDP-based ICER thresholds or value of a statistical life	The ICER thresholds are based on a country's per-capita gross domestic product (GDP) or national income. GDP-based thresholds are the most commonly cited thresholds [123, 124]. The reason for using the GDP-based threshold is that GDP is a proxy for earnings or available income. Ill health has a negative impact on these earnings and affects also the GDP.	Single or multiple baseline ICER thresholds possible (range)
Societal ICER thresholds (societal willingness to pay threshold)	The calculated threshold reflects the societal preferences and values of the relevant population groups in relation to health gains. The societal WTP for an additional health gain is the amount of budget funds or resources society is temporarily willing to give up from somewhere else to obtain the additional health gain.	Single or multiple baseline ICER thresholds possible (if societal values are considered)
Efficiency frontier approach (benchmark approach)	The most efficient combination of currently available interventions forms the efficiency frontier. A new intervention is embedded within this efficiency frontier and a potential price ceiling is calculated by using the proportional rule.	No threshold (price ceiling is calculated)

3.5 The Role of Health Economic Evaluation Evidence in the Decision-Making and Policy Process

Entscheidungsfindung muss oft widersprüchliche Ziele berücksichtigen → aufgrund institutioneller Rahmenbedingungen ist Effizienz nicht das einzige Kriterium

As already mentioned, the primary purpose of HEE is to provide health economic evidence to inform decision and policy makers in the health care system about the efficient use of resources [3, 4]. However, decision-making usually needs to take into account more than one and often contradictory goals, given the institutional conditions. Efficiency is therefore not the only criterion on which decisions can be based on [82].

2 Ansätze zur Integration von anderen Kriterien:

Two different approaches exist on how to integrate criteria beyond efficiency formally in reimbursement decisions:

- Modifying the HEE design or the threshold (threshold-modifying):
  - modifying the cost side of an ICER by choosing different perspectives for the HEE depending on the nature of the disease's costs (e.g., applying a societal perspective for diseases with a high need for informal care),
  - modifying the outcome side of an ICER by introducing equity elements such as QALY weights for different subpopulations,
  - modifying the whole CEA with equity aspects (e.g., adding a distributional cost-effectiveness analysis to the standard cost-effectiveness analysis by analysing the equity impact by social deprivation, ethnicity or sex),
  - modifying the threshold by introducing threshold modifiers (e.g., defining separate thresholds for high-severity diseases).

Design der HEE ändern oder Schwellenwert modifizieren

- Assigning the modification and weighing of different reimbursement criteria to the deliberative process of an appraisal committee after an unmodified HEE (and other domains of an assessment such as effectiveness analysis) have been completed (decision-modifying) [135].

Kriterien im Entscheidungsprozess berücksichtigen

Deliberationsprozess ist aber immer nötig, da Kriterien teils nicht quantifizierbar

While the first approach aims at quantifying efficiency-modifying aspects and values and integrates them directly into the HEE or the threshold, the second one leaves social judgments beyond efficiency and the weighing of different criteria to the deliberative process of an appraisal committee. Notably, some form of deliberation will always need to take place because not all criteria are quantifiable and directly integrated into the HEE.

beide Ansätze finden in der Praxis in verschiedenen Ländern Anwendung

Both approaches can be observed across countries (see Chapters 4.1 and 4.2), although, within the first category, the method of distributional cost-effectiveness analysis is not yet widely known within the HTA community [44]. Arguments for the first approach are that it reduces the cognitive load of appraisal committees, which may arise with a high number of criteria to be judged qualitatively, and that it increases consistency and transparency [135].

Methode zur Gewichtung von QALYs & Festlegung von Schwellenwerten potenziell noch nicht ausgereift genug

Arguments against the first approach are that the methods to weigh QALYs or the ICER threshold may not be mature enough [82] and that quantitative approaches to weighing generally have too many flaws and are therefore not recommended [135]. The challenges are twofold: Firstly, there are technical challenges. For example, equity preferences are likely to exist over several characteristics (e.g., age, severity of disease). The appropriate weight to be applied will not solely be a function of their status in each equity domain but will be determined by the interaction between these domains. It is unclear whether to handle this multiplicative, additive, or in another way. Secondly,

there are conceptual challenges. If e.g., equity-modified thresholds are applied (such as higher thresholds for more severe diseases), QALYs generated by those who bear the opportunity costs are factored down. Equity is therefore only considered in the patient group under evaluation but not in the patients that bear the higher opportunity cost resulting from a higher threshold. It is likely that the "losers" will not be equity neutral either, e.g., that the opportunity cost may fall on patients with less powerful clinical support [82].

verschiedene Ansätze zur ICER- & Schwellenwerts-Modifikation sind nicht äquivalent & können zu unterschiedlichen Entscheidungen führen

It should also be noted that the different alternatives within the first approach (modifying the ICER, modifying the threshold) are not to be considered equivalent and may lead to different decisions. An intervention that is more expensive and less effective than a comparator may become cost-effective after weighing of QALYs is applied. If, instead, the threshold is modified, such an intervention will never become cost-effective, irrespective of the threshold level [136].

Kriterien jenseits der Effizienz erfordern Analyse der Bevölkerungspräferenzen

Both approaches require investigations as to which criteria are deemed important to a population. Paulden et al. [2015] identified 19 candidate attributes that may be considered for orphan diseases (e.g., the rarity of a disease, disease severity, extent to which a disease is life-threatening, and availability of treatment alternatives). If some of those are selected to formally modify the ICER or the threshold, an additional step of attributing quantitative weights is required using different methods. For deriving distributional weights for QALYs, stated preference methods described above, such as discrete choice experiments, have been used [138]. For weighing thresholds based on disease severity, methods such as the proportional or absolute shortfall have been applied (see Chapter 4.2.2). The proportional shortfall approach considers the fraction of QALYs that people lose relative to their remaining life expectancy. The absolute shortfall approach uses the absolute reduction in future healthy life years for people with the disease compared to what people of the same age but without the disease can expect. As Round and Paulden [2018] note, to meet the demands for procedural justice, attributes that address equity concerns must eventually be subject to public debate, which may be supported by empirical research to elicit societal preferences [136].

4 Overview of Countries Using Thresholds and Modifiers in Evaluations and Decision-Making

Abschnitt 4.1: Übersicht der Länder mit Schwellenwerten, deskriptive Analyse & Länderprofile

Section 4.1 overviews countries that apply specific, generally accepted ICER thresholds or threshold ranges, so-called baseline ICER thresholds, within HEEs and/or the decision-making process. In the first step, we overview the general characteristics of the identified countries. In the second step, we descriptively analyse the threshold sample and the relationship of ICER thresholds, the HLE at birth in years, and the GDP. By analysing these relationships, we wanted to find indications …

- Whether countries with a higher ICER threshold also have a higher HLE, and
- Whether decision or policy makers in countries with a higher GDP are willing to spend more for an additional health gain.

Abschnitt 4.2: Übersicht der quant. & qual. Modifikatoren

Section 4.2 provides an overview of modifying factors (modifiers) that are used in addition to the baseline ICER thresholds. Some of these modifying factors alter the threshold value (quantitative modifiers), and some of the modifiers augment the decision-making scope by further non-health economic factors (qualitative modifiers).

4.1 Countries with Specific Thresholds

4.1.1 General Characteristics

Übersichtstabellen & Quellen im Appendix

Table A-1 in the Appendix provides an overview of all collected characteristics and identified sources.

24 von 39 identifizierten Staaten (62 %) mit Schwellenwert

In total, 24 of 39 identified countries (62%) have a threshold. Of these 24 countries, 16 (66%) are European countries. A distinction can be made between countries with either an explicit or implicit threshold value, which may or may not be reported in an existing (national) pharmacoeconomic recommendation (PER), pharmacoeconomic guideline, or pharmacoeconomic submission guideline (definition in footnote 4).

7 Länder (29 %) mit expliziten/offiziellen Schwellenwerten

Schwellenwert nur in 4 Ländern in ges.ök. LL

Seven of the 24 countries (29%) have an explicit threshold: Estonia, England and Wales, Ireland, Poland, the Slovak Republic, Slovenia, and Thailand. Only in four countries (England and Wales, Ireland, Slovak Republic, and Thailand) are thresholds reported in the identified guideline. The thresholds for the three countries with explicit thresholds not mentioned in the guidelines were identified in scientific publications, documents by HTA agencies, or official documents by country authorities.

17 Länder (71 %) mit impliziten/informellen Schwellenwerten

Seventeen of the 24 countries (71%) have an implicit threshold, of which nine countries (37.5%) have guidelines mentioning the thresholds. The thresholds of eight countries that use implicit thresholds are not mentioned in the guidelines but were identified in scientific publications, documents by HTA agencies, or official documents by country authorities.

Table 4-1 provides an overview of countries with a threshold, the threshold type (explicit or implicit), whether the guideline mentions the threshold and the type of guideline:

Länderübersicht in Tabelle

Table 4-1: Countries with either an implicit or explicit threshold mentioned/not mentioned in the guideline

Implicit threshold and not mentioned in the guideline (8 countries)	Implicit threshold and mentioned in the guideline (9 countries)	Explicit threshold and not mentioned in the guideline (3 countries)	Explicit threshold and mentioned in the guideline (4 countries)
Australia (SubG)	Brazil (PEG)	Estonia (PEG)	England and Wales (SubG)
Canada (PEG)	China (PER)	Poland (SubG)	Ireland (PER)
Greece (Not available)	Czech Republic (SubG)	Slovenia (No GL, but regulation)	Slovak Republic (PEG)
Japan (PEG)	Hungary (PER)		Thailand (Guideline not available but mentioned in some sources [139-141])
Latvia (PEG)	Netherlands (PEG)		
Norway (PEG)	Scotland (SubG)		
Portugal (PEG)	Spain (PER)		
South Korea[33] (PEG)	Sweden (PEG)		
	United States (PEG)		

Abbreviations: PEG … Pharmacoeconomic Guideline, PER … Pharmacoeconomic Recommendation, SubG … Submission Guideline

There was no indication of a threshold value for 15 of the 39 identified jurisdictions (38%). The jurisdictions with neither an implicit nor explicit threshold are Austria (PER), Belgium (PEG), Bulgaria (not available), Croatia (PER), Denmark (PER), Finland (SubG), France (PEG), Germany (PEG), Israel (SubG), Italy (PER), Lithuania (PEG), New Zealand (PEG), Singapore (PEG), Switzerland (PEG), and Taiwan (PEG).

in 15 der 39 identifizierten Länder (38 %) keine Infos zu Schwellenwerten

Eleven of the 24 countries (46%) with a threshold have a baseline threshold range or, at minimum, two thresholds as baseline thresholds:

11 von 24 Staaten (46 %) mit "Basis-Schwellenwert" bzw. -Schwellenwert-Range

- **Threshold range:** Brazil, China, Czech Republic, Hungary, England and Wales, Estonia, Greece, Scotland, USA
- **Two baseline thresholds:** Canada (non-oncology and oncology), Slovenia (two thresholds depending on the decision-making agency: Health Insurance Institute of Slovenia and Ministry of Health)

Twelve of the 24 countries (50%) are explicit in their underlying method for calculating the baseline threshold or threshold range. The majority of these twelve countries (nine countries, 75%) use a GDP-based approach for their baseline threshold or threshold range:

12 der 24 Länder (50 %) geben Methode an

9 der 12 Länder (75 %) mit BIP-basiertem Schwellenwert

- 1 x GDP threshold value: South Korea
- 1-3 x GDP threshold range: Brazil, China, the Czech Republic, Estonia, Greece
- 1.5-3 x GDP threshold range: Hungary
- 3 x GDP threshold value: Poland, Slovak Republic

[33] Unclear whether the threshold is mentioned in the GL due to language barriers.

3 der 12 Länder (25 %) mit empirischem Schwellenwert

The other three countries use some form of empirical method to calculate their thresholds. The following methods are applied in particular countries:

- Australia: ICER threshold based on ICERs matched to NICE's ICERs for similar, already submitted technologies
- Latvia: ICER threshold = ICER of new intervention ≤ ICER of already reimbursed technologies
- Spain: Empirical threshold based on previous decisions

Slowakei einziges Land, das einen expliziten Schwellenwert hat & die zugrunde liegende Methode definiert

Three of the four jurisdictions with explicit thresholds mentioned in the guideline (England and Wales, Ireland, Thailand) neither specify a theoretical nor empirical underlying method. The Slovak Republic is the only country that has an explicit threshold and defines the underlying method. The Slovak Republic uses a 3 x GDP-based threshold. Table 4-2 provides an overview of the countries classified according to the underlying method to derive the threshold.

Table 4-2: Overview of countries and the underlying methods to derive the threshold

Countries with no explicit method (12 countries)	Countries with GDP-based thresholds (9 countries)	Countries with empirical thresholds (3 countries)
Canada (CAN)	South Korea (KOR), 1 x GDP	Australia (AUS)
England and Wales (E&W)	Brazil (BRA), 1-3 x GDP	Latvia (LVT)
Ireland (IRL)	China (CHN), 1-3 x GDP	Spain (ESP)
Japan (JPN)	Czech Republic (CZE), 1-3 x GDP	
Netherlands (NLD)	Estonia (EST), 1-3 x GDP	
Norway (NOR)	Greece (GRC), 1-3 x GDP	
Portugal (PRT)	Hungary (HUN), 1.5-3 x GDP	
Scotland (SCT)	Poland (POL), 3 x GDP	
Slovenia (SVN)	Slovak Republic (SVK), 3 x GDP	
Sweden (SWE)		
Thailand (THA)		
United States of America (USA)		

Abbreviations: AUS … Australia, BRA … Brazil, CAN … Canada, CHN … China, CZE … Czech Republic, ESP … Spain, EST … Estonia, EAW … England and Wales, GRC … Greece, HUN … Hungary, IRL … Ireland, JPN … Japan, KOR … South Korea, LVT … Latvia, NLD … Netherlands, NOR … Norway, POL … Poland, PRT … Portugal, SCT … Scotland, SVK … Slovak Republic, SVN … Slovenia, SWE … Sweden, THA … Thailand, USA … United States of America

4.1.2 Descriptive Analysis of the Thresholds

Description of the Variables

Ø GDP der 24 Länder (konstant 2015): € 33 671 (2022); Ø Baseline-Schwellenwert (untere Grenze, n=23): € 28 511 (SD: € 13 406); Ø Baseline-Schwellenwert (obere Grenze, n=11): € 54 205 (SD: € 32 966); Ø HLE (n=24): 68,2 Jahre (SD: 3 Jahre)

The mean constant (2015) GDP per capita in € for the year 2022 across all 24 countries with thresholds is € 33,671 with a standard deviation (SD) of € 22,315. The country with the lowest GDP is Thailand (€ 5,962) and Ireland has the largest GDP (€ 92,451). The average baseline threshold (lower bound) across countries is € 28,511 (SD: € 13,406). Thailand has the lowest threshold (€ 4,341), and the Slovak Republic has the largest threshold with € 53,859. The mean baseline threshold (upper bound) of the eleven countries with either a baseline threshold range or multiple baseline values is € 54,205. While Brazil has the lowest upper bound threshold (€ 25,143) of the countries with a threshold range or multiple baseline threshold values, the USA have the largest threshold with € 142,450. The average HLE at birth across the 24 countries with

thresholds is 68.2 years (SD: 3 years), with Brazil having the lowest number of HLE in years (61.83) and Japan having the largest HLE at 73.40 years.

Table 4-3: Summary statistics of key figures and variables

Key figure	# of Countries	Mean	Standard deviation	Minimum	Maximum
GDP per capita constant (2015) for the year 2022 in €	24	33,671	22,315	5,962	92,451
Threshold lower bound in €	23*	28,511	13,406	4,341	53,859
Threshold upper bound in €	11	54,205	32,966	25,143	142,450
Healthy life expectancy (HLE) at birth in years	24	68.20	3.00	61.83	73.40

* *Latvia is excluded from the analysis as no specific threshold is available, only the specific method on which the threshold is based.*

Jurisdictions with a national health insurance model (NHIM) seem to have the lowest threshold on average, while jurisdictions with a Beveridge system deploy the largest thresholds. However, extreme values resulting in a large standard deviation in combination with a low sample size can lead to the inflation of the mean. A look at the median threshold shows a different picture. Jurisdictions with a Bismarck system have the lowest median threshold of € 25,000, and jurisdictions with a NHIM have the largest median (€ 26,646). The overall mean and median threshold range is between € 25,000 and € 30,000.

NHIM-Länder im Ø niedrigste Schwellenwerte & Beveridge-Länder die größten Schwellenwerte; Median zeichnet anderes Bild, da Extremwerte berücksichtigt; Spannweite (Ø & median): ~ € 25.000 & € 30.000

Table 4-4: Summary statistics of thresholds in different social security systems

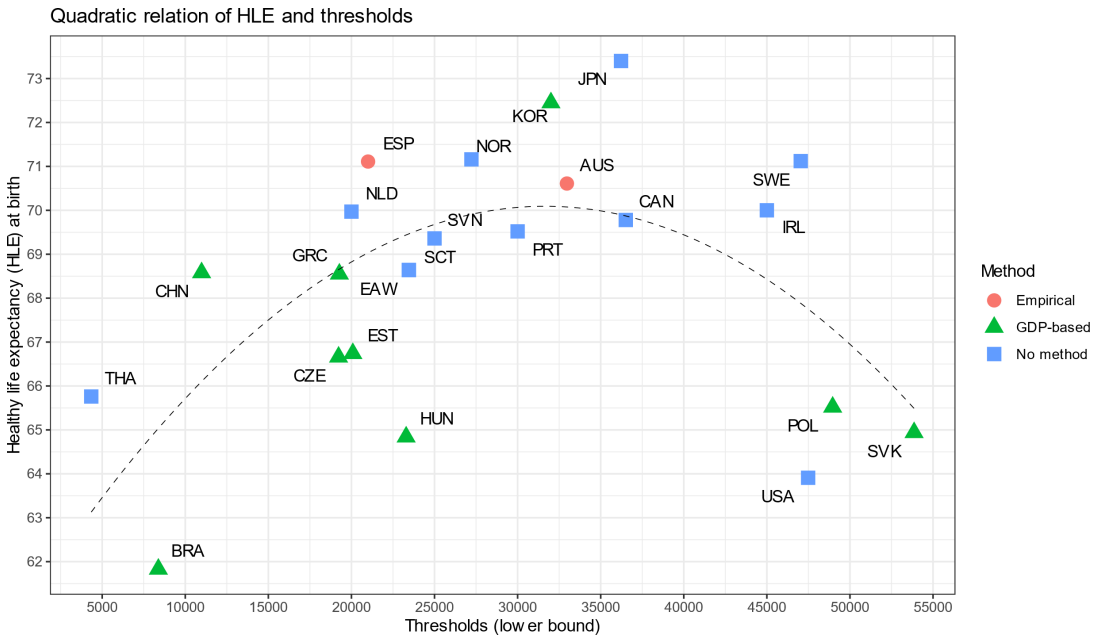
Social security system	# of Countries	Mean threshold (lower bound) in €	Standard deviation in €	Median threshold (lower bound) in €	Minimum in €	Maximum in €	Mean HLE in years	Mean GDP per capita in €
NHIM	6	26,853	7,020	26,646	19,225	36,510	68.33	25,138
Bismarck	3	27,075	8,309	25,000	20,000	36,224	70.91	35,498
Mixed	7	28,151	19,992	26,120	4,341	53,859	66.59	26,971
Beveridge	8	30,563	14,707	25,337	8,381	48,959	68.50	45,248

Relation Between HLE in Years and Thresholds

The thresholds (lower bound) in Figure 4-1 show a weak reverse U-shaped relation with HLE. The polynomial correlation is 0.41 (Multiple R^2: 0.4055) when a quadratic function of the form $y = ax^2 + bx + c$, with y being HLE and x being the threshold, is fitted to the data by a linear regression. The multiple R^2 or goodness of fit suggests that a quadratic model can partly describe the observed data relation. The remainder of HLE in years may be explained by other explanatory variables (covariates) not included in the regression model. The results of the fitted quadratic model indicate that the association of the threshold on HLE is positive until it reaches the maximum of 70.1 years at a threshold of € 31,654 and decreases when the threshold is further increased.

Zusammenhang Schwellenwert & HLE: umgekehrt U-förmig

Anpassungsgüte/Bestimmtheitsmaß legt nahe, dass quadratisches Modell beobachteten Zusammenhang teilweise beschreiben kann (multiples R^2: 0.4055)



Abbreviations: AUS … Australia, BRA … Brazil, CAN … Canada, CHN … China, CZE … Czech Republic, ESP … Spain, EST … Estonia, EAW … England and Wales, GRC … Greece, HUN … Hungary, IRL … Ireland, JPN … Japan, KOR … South Korea, LVT … Latvia, NLD … Netherlands, NOR … Norway, POL … Poland, PRT … Portugal, SCT … Scotland, SVK … Slovak Republic, SVN … Slovenia, SWE … Sweden, THA … Thailand, USA … United States of America

Figure 4-1: Relation between healthy life expectancy (HLE) and thresholds fitted a quadratic function

Analyse nach unterschiedlichen Schwellenwertmethoden → unterschiedliche Verlaufsformen

Different patterns for the data can be observed (Figure 4-2) once the relation between HLE and thresholds is plotted separately for each underlying threshold method. No clear relation can be inferred for empirical thresholds as there are only two countries, excluding Latvia, with specific empirical thresholds. The relation between GDP-based thresholds and HLE still resembles a reversed U-shaped structure, although the pattern is weaker compared to the analysis with the full data set as it has a smaller polynomial correlation (Multiple R^2: 0.3753).

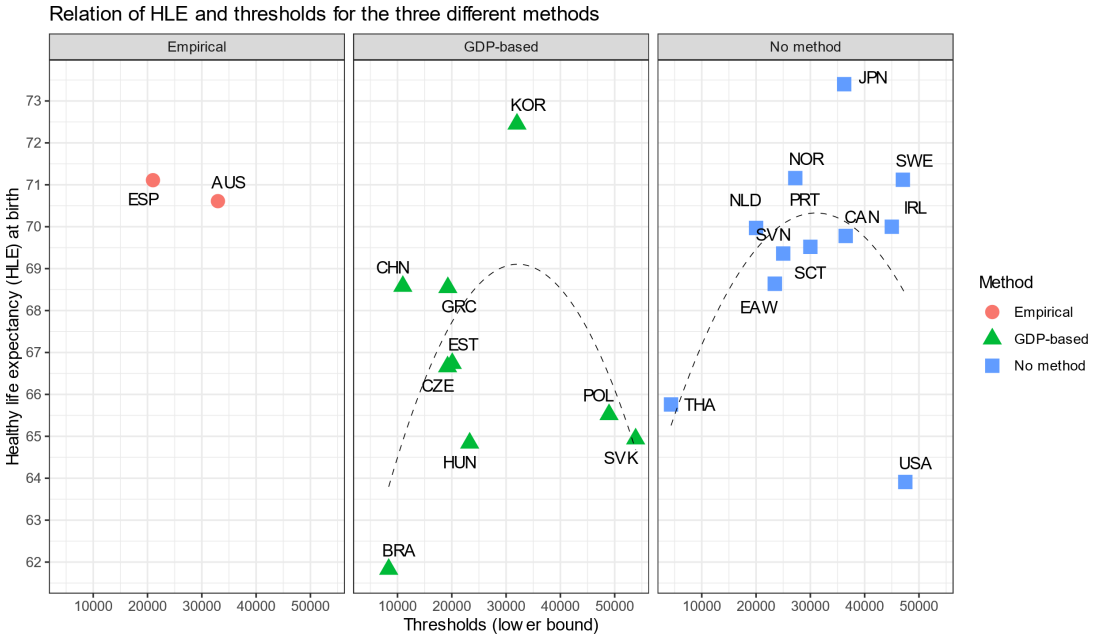
kein U-förmiger Zusammenhang für „methodenfreie" Schwellenwerte & HLE

A quadratic model does not seem appropriate for describing the relation between HLE and thresholds without a specific underlying method. The relation between thresholds without an underlying method and HLE is more likely to be explained by consideration of a power function component with an exponent between 0 and 1 in the model (e.g. a square root function). If the USA were dropped, the relation would become even more apparent.

Analyse "methodenfreier" Schwellenwerte ohne USA inkl. Quadratwurzelfunktion → multiples R^2: 0.61

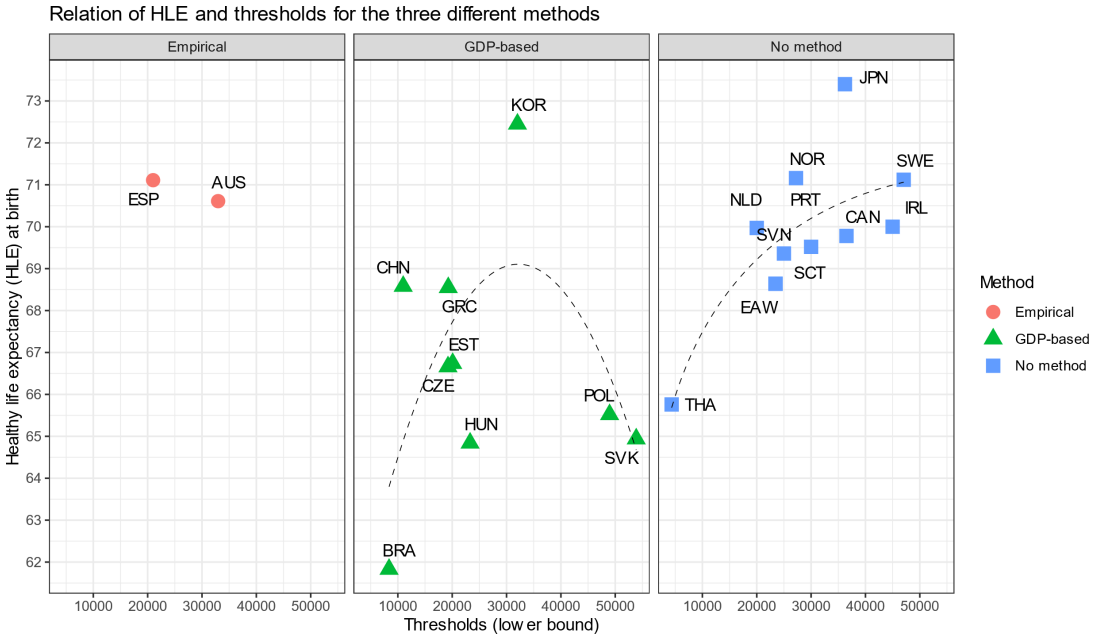
In Figure 4-3, the USA are excluded from the underlying data set, and a function including a square root term is plotted to indicate the relation between HLE and the thresholds. The fitted linear regression model with the square root term[34] seems more appropriate for explaining the relation between no-method thresholds and HLE. A linear regression including the square root of the threshold gives a coefficient of multiple correlation of approximately 0.61 (Multiple R^2: 0.6093).

[34] $y = a\sqrt{x} + bx + c$ with y being HLE and x being the threshold.



Abbreviations: AUS … Australia, BRA … Brazil, CAN … Canada, CHN … China, CZE … Czech Republic, ESP … Spain, EST … Estonia, EAW … England and Wales, GRC … Greece, HUN … Hungary, IRL … Ireland, JPN … Japan, KOR … South Korea, LVT … Latvia, NLD … Netherlands, NOR … Norway, POL … Poland, PRT … Portugal, SCT … Scotland, SVK … Slovak Republic, SVN … Slovenia, SWE … Sweden, THA … Thailand, USA … United States of America

Figure 4-2: Relation between healthy life expectancy (HLE) and thresholds by method fitted a quadratic function for GDP-based and No method thresholds



Abbreviations: see Figure 4-2

Figure 4-3: Relation between healthy life expectancy (HLE) and thresholds by method fitted a quadratic function (GDP-based thresholds) and a linear model with a square root function (No method thresholds) excluding the USA

The relation between HLE in years and no-method-thresholds described by a power function with an exponent between 0 and 1 is reminiscent of the production function with decreasing returns to scale from neoclassical microeconomics. This specific relation indicates that with increasing inputs, outputs increase, but with decreasing increments, efficiency decreases. In the case of the HLE and threshold relation, this means that with an increasing threshold amount, HLE increases in years but with a diminishing rate.

Beziehung erinnert an Produktionsfunktion mit abnehmenden Skalenerträgen aus (neoklassischer) Mikroökonomie

Relation Between Thresholds and GDP per Capita

A clear relation between the thresholds and GDP per capita cannot be inferred when a linear regression is fitted with the whole data set. A linear regression model with a square root term of the GDP per capita gives a goodness of fit of approximately 0.24 (Multiple R^2: 0.2431). This correlation means that the GDP per capita can only partly explain the relation with the threshold level given the proposed model. Other covariates, not included in the linear regression, may explain more threshold variation across jurisdictions. For example, the underlying method or preferences towards more health expenses could impact the magnitude of the threshold. However, the thresholds of Slovakia and Poland, both GDP-based thresholds, may affect linear regression results and could be responsible for the "low" goodness of fit of the estimated model. Before we analyse the complete data set without Slovakia and Poland, we investigate the relation of the GDP per capita and thresholds for each underlying threshold method separately. This analysis will help us to get a fuller picture of the underlying threshold methods and provide a more complete picture of potential "extreme values".

Zusammenhang BIP pro Kopf & Schwellenwert im gesamten Sample nicht eindeutig (R^2: 0.24)

weitere Variablen könnten mehr Variation erklären (bspw. zugrundeliegende Kalkulationsmethode & Präf. hinsichtlich höherer Gesundheitsausgaben)

→ Analyse nach unterschiedlichen Schwellenwertmethoden

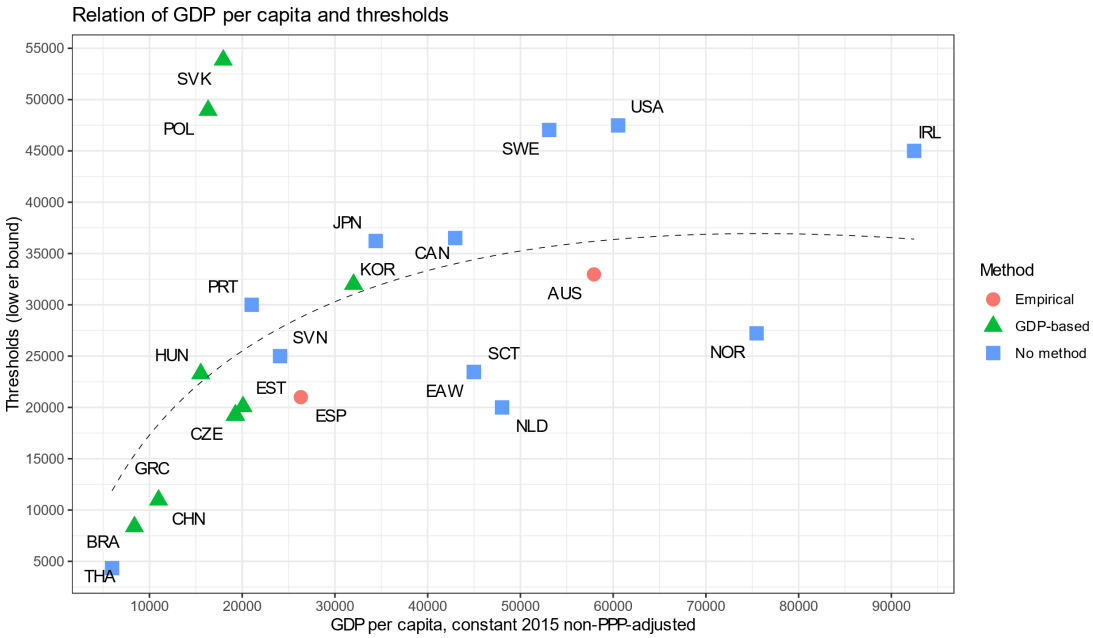


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Figure 4-4: Relation between thresholds (lower bound) and GDP per capita fitted a linear regression including a power function term (square root)

Zusammenhang zwischen BIP & BIP-basierten Schwellenwerten nicht durch eine einfache 1:1 lineare Funktion erklärbar (multiples R^2: 0.12)

If the relation between the GDPs per capita and thresholds is plotted separately for each method (Figure 4-5), the relations become more apparent. The relation of GDP-based thresholds is self-explaining. The larger the GDP per capita, the larger the GDP-based threshold. However, a simple one-to-one linear function cannot describe the relation of GDP per capita and the thresholds. When fitting a linear regression with a linear functional form for the whole set of countries with GDP-based thresholds, the goodness of fit is only approximately 0.12 (Multiple R^2: 0.1242), and the correlation between these two variables is only 0.35.

"BIP-Faktor" des Schwellenwerts hat Einfluss auf den Zusammenhang

Polen & Slowakei haben bspw. einen Faktor von 3

linearer Zusammenhang ohne Polen & Slowakei eindeutiger (multiples R^2: 0.86)

The cause for this weak linear relation is that the level of the GDP-based threshold is also affected by the "GDP factor". The GDP factor is the factor by which the GDP is multiplied, resulting in the specific threshold. The larger the GDP factor, the larger the final threshold. The threshold value for Slovakia and Poland is an example of the impact of the GDP factor on the threshold. Slovakia and Poland have a larger threshold factor (3 x GDP) compared to the other countries with GDP-based thresholds. This is why these two countries have by far the highest thresholds (SVK: € 53 859, POL: € 48,959) compared to the other countries with GDP-based thresholds but also compared to countries with non-GDP-based thresholds. If these two countries are dropped from the data, the goodness of fit is 0.86 (Multiple R^2: 0.8615), and the correlation is approximately 0.93. There is no complete correlation (correlation of 1), because Hungary has a GDP-factor of 1.5. Otherwise, the fitted line in Figure 4-5 for GDP-based thresholds would have a slope of one on the 45°-degree line of the coordination system (complete correlation of threshold and GDP).

Analyse BIP pro Kopf & "methodenfreier" Schwellenwerte inkl. Quadratwurzelfunktion (multiples R^2: 0.48): → mit steigendem BIP pro Kopf erhöht sich der Schwellenwert, allerdings mit abnehmender Rate

The fitted linear regression model with the square root is partly associated with the relation of no-method thresholds and GDP per capita. A linear regression including the square root gives a coefficient of multiple correlation of approximately 0.48 (Multiple R^2: 0.4815). The no-method-threshold level may be further explained by covariates not included in the linear regression model. Although the linear model cannot fully explain the variation, the GDP per capita may also play a role in the threshold level in countries that do not use a specific method. With an increasing GDP per capita, the threshold level increases but with a diminishing rate.

Analyse ganzer Datensatz ohne Polen & Slowakei: Erklärungskraft nimmt nur geringfügig zu (multiples R^2 von 0.24 zu 0.29)

→ andere Faktoren, wie länderspezifische Präf. Bei Gesundheitsausgaben oder sozioökonomische Faktoren, potenziell auch relevant (vor allem in „einkommensstarken" Staaten)

If Slovakia and Poland are excluded from the complete data set and a linear regression model with a square root term is fitted to the data, the model's explanatory power only slightly increases. The coefficient of multiple correlation is 0.29 (Multiple R^2: 0.2885) compared to 0.24 for the whole data set. The variation of threshold values across countries increases, particularly as GDP per capita rises. This observation and the low goodness of fit of the fitted model provide further evidence that other factors play a role in explaining the variation in thresholds. Countries may not only set the threshold based on GDP. Country-specific preferences, values or socio-economic factors not included in the linear regression also seem to play a role. These factors may be more influential in "higher-income" countries that do not have an underlying method to determine the threshold. The variation of the threshold conditional on the GDP per capita increases for these countries, and the relation between the thresholds and GDP per capita is also weaker for higher-income countries (see Figure 4-6).

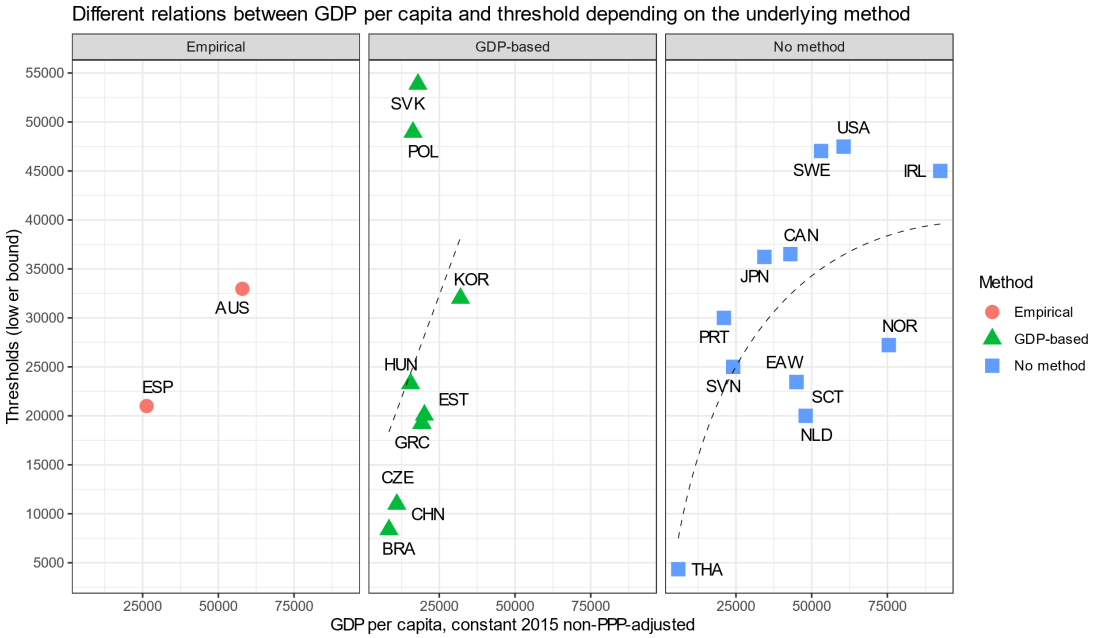

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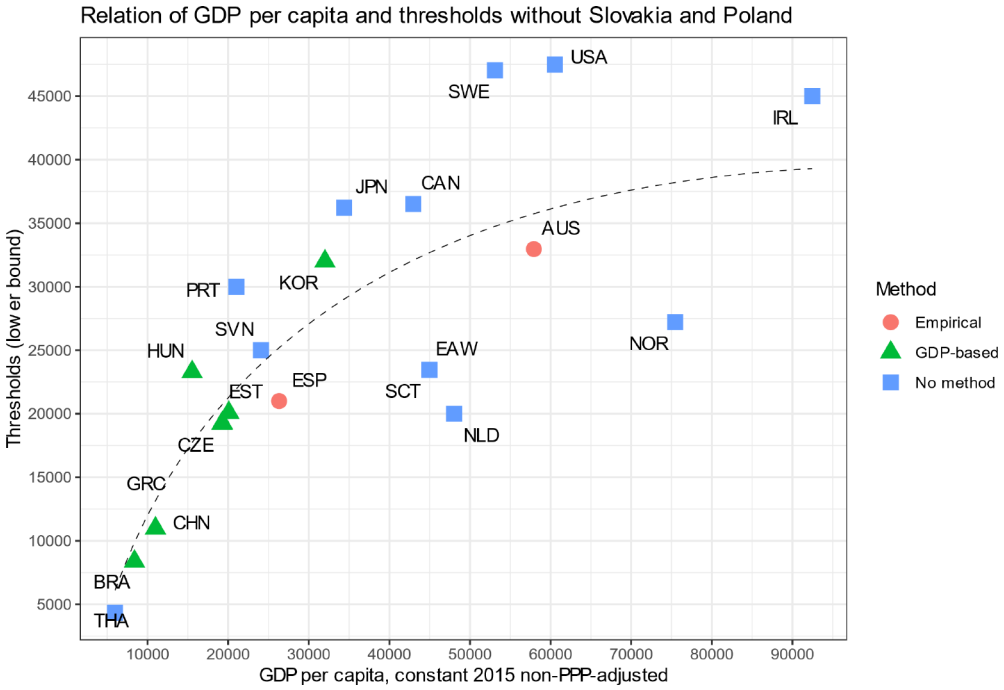
Figure 4-5: Relation between thresholds (lower bound) and GDP per capita by method fitted a linear function (GDP-based thresholds) and a square root function (No method thresholds)



Abbreviations: see Figure 4-5

Figure 4-6: Relation between thresholds (lower bound) and GDP per capita fitted a linear regression including a power function term (square root) excluding Slovakia and Poland

The following subsection describes each country with an existing threshold separately. These countries differ in their system characteristics and use different calculation methods for their ICER thresholds that impact the setting of the threshold and application of HEE.

nächster Abschnitt: detailierte Länderprofile

4.1.3 Country Profiles

Data on the type of product or intervention to which the threshold applies, whether it is a medicinal drug, medical device, or general health care intervention, were taken from guidelines, identified publications and mentioned in the respective country profiles. However, this information is only indicative, as only incomplete information was available. In principle, however, the ICER thresholds are mainly used to make a reimbursement decision for medicinal products.

Art der Intervention, für die der Schwellenwert gilt, aufgrund von Mangel an Infos nur indikativ

Australia

The Pharmaceutical Benefits Advisory Committee (PBAC) submission guideline does not report on a specific threshold. However, as Zhang and Garau [2020] outline, a threshold has been estimated by analysing PBAC decisions in the past and matching these ICERs with NICE's ICERs of submitted technologies [142]. Based on this historical analysis, the ICER threshold is around AUD 50,000 (€ 32,966) per QALY. Paris and Belloni [2013] report for Australia that technologies with an ICER greater than AUD 75,000 (€ 49,449) per QALY were rarely recommended [101]. Thokala et al. [2018] report that technologies with an ICER greater than AUD 45,000 (€ 29,670) per QALY were recommended only in rare circumstances [101]. A publication by Edney et al. [2018] empirically estimated an ICER threshold to publicly fund new health technologies of AUD 28,033 (€ 18,483) per QALY gained. The publication also mentions that summary documents from the PBAC have referred to the need to bring pharmaceutical prices down so that ICERs are reduced to a value between AUD 45,000 (€ 29,670) and AUD 75,000 (€ 49,449) [144]. The implicit ICER threshold of AUD 50,000 (€ 32,966) per QALY cited in the Zhang and Garau [2020] publication lies within this interval.

Australische Einreichungs-LL führt keinen expliziten Schwellenwert an

impliziter Schwellenwert: € 32.966 pro QALY

Brazil

Brazil has an implicit threshold range of 1-3 x GDP per capita. This range is equal to RBL 45,591-136,774 (€ 8,381-25,143). The Brazilian pharmacoeconomic guideline states that *"Technologies with an ICER (monetary unit/DALY avoided) of less than one times the GDP per capita would be considered very cost-effective; up to three times the GDP per capita, still cost-effective; those with an ICER above three times the GDP per capita would be considered not cost-effective"* [145, p. 84]. This definition corresponds to the WHO-CHOICE definition of cost-effectiveness.

implizite Schwellenwert-Range in BRA: € 8.381-25.143 pro DALY → entspricht WHO-Definition von 1-3 x BIP pro Kopf pro DALY

Canada

The implicit threshold in Canada is assumed to be CAD 50,000 (€ 36,510) for non-oncology medicines and CAD 100,000 (€ 73,019) for oncological drugs. These threshold values are based on information from an interview in Zhang and Garau [2020]. However, the authors report that these thresholds are outdated as new guidelines by the Patented Medicines Price Review Board (PMPRB) were developed during the writing of their report [146]. The outdat-

implizite Schwellenwerte in CAN: € 36.510 pro QALY für nicht-onkologische Medikamente & CAD € 73.019 pro QALY für Onkologika

ed thresholds were not reported in the old pharmacoeconomic guidelines by Canada's Drug Agency (CDA-AMC), the former Canadian Agency for Drugs and Technologies in Health (CADTH) [147]. Also, Thokala et al. [2018] report, based on Griffiths and Vadlamudi [2016], that the threshold of CAD 50,000 (€ 36,510) per QALY is not consistently applied.

neue LL schlägt ein neues Bewertungskonzept vor:

The new guidelines state that the ICER will be compared against a so-called *Pharmacoeconomic Value Threshold (PVT)* based on four *Therapeutic Criteria Levels (TCL)* [146]:

"Pharmacoeconomic Value Threshold" auf Basis von 4 "Therapeutic Criteria Levels"

- Level 1 (CAD 200,000 per QALY [€ 146,039]): *"The patented medicine is the first medicine to be sold in Canada that effectively treats a particular illness or effectively addresses a particular indication".*
- Level 2 (CAD 150,000 per QALY [€ 109,529]): *"The patented medicine provides a considerable improvement in therapeutic effect, relative to other medicines sold in Canada, in a clinically impactful manner".*
- Level 3 (CAD 150,000 per QALY [€ 109,529]): "*The patented medicine provides moderate absolute improvement in therapeutic effect relative to other medicines sold in Canada".*
- Level 4 (CAD 100,000 per QALY [€ 73,019]): *"The patented medicine provides slight or no improvement relative to other medicines sold in Canada".*

unklar ob neues Bewertungskonzept & Schwellenwerte aus neuer LL rechtlich implementiert sind & angewendet werden

The criteria descriptions of each level are more extensive and are reported in the guideline [146]. For example, Level 2 and 3 medicines have the same threshold, but the final prices of medicines from these two different levels differ regarding the reduction cap applied to the maximum list prices used in price negotiations. The new PMPRB guidelines are published, but whether they are in force now is unclear from their official website and the CADAMC's/CADTH's website. According to a newsletter article, the guidelines have not been legally implemented so far[35]. Two other publications estimated a threshold of CAD 80,000 (€ 58,415) per QALY for the period 2003-2007 [143].

China

HTA rechtlich verankert in CHN

In 2016, China launched a new round of reform of the national healthcare system, the Healthy China 2030 Plan, which also stated that HTA and pharmacoeconomic evaluations of pharmaceutical products will play a more central role in resource allocation [151-153]. Since 2019, HTA is legally mandated in reimbursement decisions and price negotiations between the National Healthcare Security Administration and pharmaceutical companies [115]. China is among the countries using 1-3 x GDP per capita per QALY as a threshold range. This range corresponds to RMB 77,630-232,890 (€ 10,982-32,947) per QALY. Although the threshold value is specified in the pharmacoeconomic recommendation from 2020, the threshold values are only applied informally (implicit threshold values) [151]. A publication from 2024 evaluated a WTP threshold of RMB 128,000 (€ 18,108) per QALY for chronic diseases, RMB 149,500 (€ 21,150) per QALY for rare diseases, and RMB 140,800 (€ 19,919)

implizite Schwellenwert-Range: € 10.982-32.947 → entspricht WHO-Definition von 1-3 x BIP pro Kopf aber pro QALY & nicht DALY …

[35] *"The coming-into-force of the amended Patented Medicines Regulations ("Regulations") has been further delayed past January 1, 2022. Consequently, the new Guidelines will not be coming into effect on January 1, 2022."* [149]. A newsletter article published by the Canada's National Observer from October 26th 2023 reported that a delay was intended to give more time for industry groups to participate, which caused a major disagreement at the agency and culminated in the resignation of several board members and the executive director [150].

per QALY for terminal diseases. These thresholds correspond to 1.76, 2.06 and 1.94 times the GDP per capita in China [154]. A publication by Ochalek et al. [2020] estimated a threshold range of RMB 27,923-52,247 (2017 RMB) (€ 3,950-7,391) per DALY averted, corresponding to 47-88% of GDP per capita. This range is far below the lower bound of the WHO recommendation.

… weitere Schätzungen zu Schwellenwerten ergaben teils niedrigere Werte, e.g., 47-88 % des BIP pro Kopf pro DALY

Economic development in China is asymmetrical, and GDP per capita between the various regions varies a lot. Therefore, the pharmacoeconomic recommendation proposes that a pharmacoeconomic evaluation at the national level should use national GDP per capita as the threshold. A pharmacoeconomic assessment for regional health policies should use local GDP per capita [151].

ökonomische Entwicklung in CHN asymmetrisch → LL-Empfehlung: Schwellenwerte basierend auf regionalen BIP pro Kopf

Czech Republic

Until now, the Czech Republic has no formal HTA institute and no explicit threshold in place. The State Institute for Drug Control (SÚKL) is the administrative authority with surveillance and decision-making powers. Since 2013, when the SÚKL methodology document for cost-effectiveness assessment (SP-CAU-028) was published, the WHO-CHOICE threshold (1-3 x GDP per capita) and methodology were adopted as a valid analysis framework. This range corresponds to CZK 472,292-1,416,876 (€ 19,225-57,676) per QALY. The most recent Czech submission guideline by SÚKL reports the use of a threshold of CZK 1.2 million (€ 48,848) per QALY. The guideline states that CZK 1-1.2 million (€ 40,706.67-48,848) per QALY is an acceptable threshold, which is also within the GDP-based threshold [155]. In borderline cases, i.e. ICER between CZK 0.9-1.2 million (€ 36,636-48,848) per QALY, greater account will be taken of the uncertainties associated with the input data (sensitivity analysis) [155]. The Czech Pharmacoeconomic Society (CFES) guideline also mentions the WHO-CHOICE threshold approach as adequate guidance [156].

impliziter Schwellenwert in CZE → WHO-CHOICE Schwellenwert (1-3 x BIP pro Kopf): € 19.225-57.676 pro QALY

ges.ök LL der Gesellschaft für Pharmakoökonomie (CFES) erwähnt den WHO-Ansatz als angemessen

England and Wales

England and Wales are among the seven jurisdictions with an explicit threshold (range). The threshold range is £ 20,000 to 30,000 (€ 23,453-35,180) per QALY. Above the lower bound of the ICER threshold range of £ 20,000 (€ 23,453) per QALY, the decision committee consults the upper bound of the threshold range (£ 30,000/€ 35,180). Decisions about the acceptability of the technology as an efficient use of NHS resources will then also specifically consider the degree of certainty and uncertainty of the ICER, uncaptured benefits and non-health factors, and innovations in their reimbursement decision [8, 17, 157, 158].

E&W mit explizitem Schwellenwert-Range: € 23.453-35.180 per QALY

However, NICE's ICER threshold range has little theoretical and empirical basis:

Schwellenwert-Range aber ohne theoretische & empirische Basis

> *"The committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost-effective or below which it would. Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies. NICE does not have complete information about the costs and QALYs from all competing healthcare programmes to define a precise maximum acceptable ICER. However, NICE considers that it is most appropriate to use a range as described in […]. Also, consideration of the cost-effectiveness of a technology is necessary but is not the only basis for decision-making. Consequently, NICE considers technologies in relation to this*

> *range of maximum acceptable ICERs, so that the influence of other factors on the decision to recommend a technology is greater when the ICER is closer to the top of the range."* – National Institute for Health and Care Excellence (NICE) [2023, p. 173]

The DHSC in the UK uses a cost per QALY "at the margin" (marginal product of health) of £ 15,000 per QALY in their impact assessments. This value is based on the estimate by Claxton et al. [2015] [159]. The estimate and the proposed cost per QALY "at the margin should represent "true" opportunity cost in the sense of average displacement of health within a fixed budget as mentioned in Chapter 3.4.1 on Empirical ICER Thresholds in a Fixed Budget Setting: Opportunity [98].

Estonia

impliziter Schwellenwert in EST → WHO-CHOICE Schwellenwert (1-3 x BIP pro Kopf): € 20.084-60.252 pro QALY

According to Garcia-Mochon et al. [2019], Estonia has an implicit threshold based on 1-3 x GDP per capita (€ 20,084-60,252) per QALY. However, this threshold approach is not mentioned in the Baltic pharmacoeconomic guideline from 2002. A survey among Eastern European countries reports that Estonia has an "official" threshold of € 20,000 per QALY. Whether this amount is explicitly or implicitly applied cannot be validly inferred because only the abstract of the publication with limited information on the methods is available [160]. Another publication from 2018 states that for a positive reimbursement decision, the ICER per QALY must be below € 40,000 [161].

Greece

impliziter Schwellenwert in GRC → WHO-CHOICE Schwellenwert (1-3 x BIP pro Kopf): € 19.273-57.820

The current HTA process in Greece only includes medicinal products until now. A Committee for the Negotiation of Medical Devices' Fees and Prices does exist but is not involved in assessing new medical devices [162]. Mavrodi and Aletras [2020] report that Greece adopts the GDP-based approach by the WHO of 1-3 x GDP per capita (€ 19,273-57,820) per QALY. In their publication, they estimated a potential ICER threshold for Greece by a contingent valuation approach. The mean WTP per QALY is € 26,280 per QALY. The estimated WTP per QALY falls within the threshold GDP-based threshold range. Considering outliers by a 5% trimming approach, the WTP per QALY decreased to € 14,862 [163]. As for Estonia, a survey reports that Greece has an unofficial threshold of € 30,000 per QALY. Whether this amount is applied cannot be validly inferred because only the abstract of this publication with limited information on the methods is available [160]. According to expert information, Greece is currently introducing a new HTA process [164].

Hungary

impliziter BIP-basierter Schwellenwert in HUN

The Hungarian pharmacoeconomic recommendation issued by the Ministry of Human Resources report on a threshold range of 1.5-3 x GDP per capita per QALY [165]. This corresponds to a range of HUF 9,113,953-18,227,907 (€ 23,292-46,584) per QALY.

eigenes Berechnungsschema für 1.5-3 x BIP pro Kopf bzw. € 23.292-46.584 pro QALY

The recommendation has the following rules for non-rare diseases:

- If the value of the excess health gain, i.e., 1 minus the ratio of the QALYs of the comparator and the QALYs of the technology under investigation, is between 0.00 and 0.25, the threshold is 1.5 x GDP per capita.

- If the value of the excess health gain, i.e., 1 minus the ratio of the QALYs of the comparator and the QALYs of the technology under investigation, is between 0.25 and 0.60, the threshold is twice the GDP per capita.
- If the value of the excess health gain, i.e., 1 minus the ratio of the QALYs of the comparator and the QALYs of the technology under investigation, is between 0.60 and 1.00, the threshold is 3 x GDP per capita.

An older publication states that health technologies are declared as cost-effective under the threshold of 2 x GDP per capita per QALY, and proclaimed not cost-effective if the ICER is higher than 3 x GDP per capita per QALY [166].

Ireland

expliziter Schwellenwert in IRL in LL: € 45.000 pro QALY

Ireland also has an explicit ICER threshold for pharmaceutical interventions, which is also reported in the pharmacoeconomic guideline by the Health Information and Quality Authority (HIQA) [167]. The threshold is € 45,000 per QALY.

aber ohne theoretische & empirische Basis

As the threshold in England and Wales, HIQA's threshold has little theoretical and empirical basis:

> *"Historically, the threshold has varied between €20,000 and €45,000 per QALY, although reimbursement below these levels was not guaranteed, and technologies above these thresholds have been adopted. For reporting purposes, it is pragmatic to report the probability of cost-effectiveness at thresholds of €20,000 and €45,000 per QALY. It is important to note that these thresholds have not been derived empirically. While consideration of the cost-effectiveness of a technology is necessary, it is not the sole basis for decision- making."* – Health Information and Quality Authority (HIQA) [2020, p. 55]

Erstattung garantiert für ICER < € 45.000 pro QALY

Meanwhile reimbursement is guaranteed for new medicinal products with an ICER below the upper threshold of € 45,000 [168]. Reporting of the probability of cost-effectiveness at thresholds of € 20,000 and € 45,000 per QALY is required in HIQA's evaluations [167].

Japan

Evidenz aus CEA seit 2019 verpflichtend in JPN, allerdings kein expliziter Schwellenwert

Japan initiated an HTA process in 2019 [1]. Since April 2019, submission of cost-effectiveness evidence for selected pharmaceuticals and medical devices to the Central Social Insurance Medical Council (Chuikyo) is obligatory [169]. Chuikyo reached a consensus to use JPY 5 million (€ 36,224) per QALY as the ICER threshold. If the ICER of a product is less than JPY 5,000 000 (€ 36,224) per QALY, its price is not adjusted. If the ICER is between JPY 5 million (€ 36,224) and 10 million (€ 72,448) per QALY, the price adjustment rate increases stepwise. The price is adjusted at the maximum rate if the ICER is over JPY 10 million (€ 72,448) per QALY [170].

impliziter Schwellenwert: € 36.224 pro QALY, darüber stufenweise Anpassung des Preises

A study in 2013 examined the WTP value for one additional QALY in a sample of 2,400 respondents. The WTP ranged from JPY 2,000,000 to 8,000,000 (€ 14,490-57,958) per QALY, depending on the severity of health states [171].

Latvia

Budgetfolgenanalyse & CEA in LVT verpflichtend für Erstattung

expliziter, „empirischer" Schwellenwert, aber kein genauer Wert verfügbar

ICER neue Intervention ≤ ICER für bereits erstattete Arzneimittel = Schwellenwert

As for Estonia, the Baltic pharmacoeconomic guideline does not report on a specific threshold. Silins and Szkultecka-Debek [2017] report that cost-effectiveness and budget impact analyses are required for reimbursement decisions. The authors refer to a regulatory document that does not mention an explicit threshold. However, the regulation states that *"an ICER threshold is defined as the ICER for additional life-year gained, which does not exceed the ICER for medicinal products and medical devices already included in the positive reimbursement list"* [172, p. 76] (ICER of new intervention ≤ ICER of pharmaceuticals already reimbursed). The already mentioned survey by Augustyńska et al. [2022] among Eastern European countries reports that Latvia has an official threshold of € 52,300 per QALY. Whether this amount is explicitly or implicitly applied cannot be validly inferred because only the abstract of this publication with limited information on the methods is available [160].

Netherlands

CEA seit 2005 fester Bestandteil bei Erstattungsentscheidungen

impliziter Schwellenwert in NL: € 20.000 pro QALY

The Netherlands have no explicit threshold [1]. However, since 2005, CEA has become an integral part of the Dutch medicine reimbursement system and the Dutch National Health Care Institute (Zorginstituut Nederland; ZIN) has set an implicit threshold range depending on the burden-of-illness in their guideline [109, 173, 174]. The baseline threshold is € 20,000 per QALY, and the maximum reference value is € 80,000 per QALY gained depending on other factors, such as severity of disease (see Chapter 4.2 Countries with Modifiers) [109].

wissenschaftliche Publikationen schätzen ähnlichen Wert

The authors van Baal et al. [2019] estimated a k-threshold of € 41,000 based on the marginal returns to medical care. This threshold almost corresponds to the suggested implicit baseline threshold. Another publication by Stadhouders et al. [2019] estimated a threshold of € 73,600 per QALY (95% CI: € 53,000 to € 94,000). This estimate is greater than the baseline threshold and reflects almost to the maximum reference threshold of € 80,000 for reimbursement decisions considering further factors [175].

Norway

impliziter Schwellenwert von € 27.221 per QALY in NOR

Zhang and Garau [2020] report that Norway had previously an indicative threshold of NOK 500,000 (€ 49,493) per QALY, which was not always used. However, another publication from 2016 reports that thresholds have never been examined and approved by the parliament [176]. The interview by Zhang and Garau [2020] with a representative of the Norwegian Institute for Public Health (NIHR) revealed that a current implicit threshold of NOK 275,000 (€ 27,221) per QALY is applied. The Norwegian pharmacoeconomic guideline does not mention any specific threshold but reports a method to account for disease severity within the application of informal thresholds [177]. Ottersen et al. [2016] report on a similar approach and mention that the baseline threshold is NOK 250,000 (€ 27,221) per QALY. However, the authors do not mention the method to derive the baseline threshold. They state that the method follows an "opportunity cost approach" based on the condition- or disease-associated health loss.

wissenschaftliche Publikationen schätzen einen ähnlichen Wert

Poland

expliziter, BIP-basierter Schwellenwert in POL: € 48.959 pro QALY (3 x BIP pro Kopf)

Schwellenwert für Erstattungsentscheidungen für Medikamente & medizinische Geräte

In Poland, decision makers apply an explicit threshold, which is also set by law (Reimbursement Act) [1]. The threshold is 3 x GDP per capita, which would be approximately PLN 229,428 (€ 48,959) per QALY according to this report's calculation method. However, Zhang and Garau [2020] report a threshold of PLN 146,937 (€ 31,356) per QALY (2016 Local currency unit), and Orlewska et al. [2022] report a threshold of PLN 147,024 (€ 31,375) per QALY. The difference may be due to the difference in the used GDP approach (current versus constant) and the different exchange rates. The threshold is not mentioned in the submission guideline by the Agency for Health Technology Assessment and Tariff System (AOTMiT) [179]. The threshold is applied to medicinal products and medical devices [1].

Portugal

impliziter Schwellenwert in POR: € 30.000 pro QALY

A study on the clinical impact and cost-effectiveness of routine HIV Screening in Portugal states, "*Anecdotal evidence suggests that the Portugues National Authority of Medicines (Infarmed) adopts an informal threshold of € 30,000/QALY in determining whether a given pharmaceutical intervention is cost-effective. This threshold is inspired by the United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines*" [180]. A publication by Laires et al. [2015] investigating the cost-effectiveness of statin monotherapy also states that *"Considering the Portuguese cost-effectiveness willingness-to-pay threshold of €30,000/QALY, adding ezetimibe vs switching to rosuvastatin would be a cost-effective use of resources in Portugal"*. A CUA of genetic polymorphism universal screening in colorectal cancer prevention set the threshold at € 44,870, which complies with the US ICER threshold of USD 50,000 (€ 47,483) per QALY [182]. The Portuguese guideline states that the presentation of health economic results should consider opportunity cost using threshold ranges between € 10,000 and € 100,000 per QALY [183].

Scotland

SCT selbe Schwellenwert-Range wie E&W, aber nicht explizit: € 23.453-35.180 per QALY

Scotland applies the same threshold range of £ 20,000-30,000 (€ 23,453-35,180) per QALY as England and Wales. However, the Scottish Medicines Consortium (SMC) does not define this range as an explicit threshold range; instead, it refers to NICE's threshold. The Scottish submission guideline mentions the threshold lacks the same theoretical and empirical justifications as the threshold in England and Wales [184].

South Korea

impliziter, BIP-basierter Schwellenwert in KOR: € 32.006 per QALY → 1 x BIP pro Kopf

South Korea does not have an explicit threshold. Zhang and Garau [2020] report that South Korea uses a 1 x GDP per capita threshold, which was reported in Bae et al. [2018]. This corresponds to KRW 43,466,198 (€ 32,006) per QALY using the World Bank data[36]. A publication from 2022 estimated the social value of a QALY by a WTP approach at the national level using EQ-

[36] Zhang and Garau [2020] report a value of KRW 25,000,000 (€ 18,408.48) which was and should reflect the 1 x GDP per capita threshold reported in Bae et al. [2018]. However, the converted 1 x GDP per capita threshold using the World Bank data is KRW 43,466,198 (€ 32,006). For the analysis, we used this value based on our GDP per capita calculation.

5D scenarios. The WTP ranged from KRW 15 million (€ 11,045) per QALY to KRW 40.28 million (€ 29,660) per QALY depending on the severity of the diseases (mild symptoms, moderate symptoms, severe symptoms, severe terminal disease, immediate death) [186]. Another publication from 2010 elicited a WTP per QALY of KRW 68,000,000 (€ 50,071) [171]. Whether the threshold is mentioned in the guideline is unclear due to language barriers [187].

Slovak Republic

expliziter, BIP-basierter Schwellenwert in SVK: € 53.859 pro QALY

→ 3 x BIP pro Kopf von vor 2 Jahren

neues Medikament muss mindestens 0,33 QALYs hinzufügen

The Slovak Republic is among the jurisdictions with an explicit threshold. HTAs for new medicinal drugs and medical devices must be completed within 130 days excluding time for "clock stops". The Ministry of Health of the Slovak Republic approved the Act. No 363/2011 in 2022 governing access to medicines and innovation for Slovak patients. This act set the baseline threshold value to 3 x GDP per capita (€ 53,859) [188]. The threshold for orphan drugs and Advanced Therapy Medicinal Products (ATMPs) was set to 3.5 to 10 x GDP per capita [189]. For most drugs, the threshold is set at 3 x GDP per capita of two years ago per QALY, if the drug adds at least 0.33 QALYs. In the case of a lower contribution, 2 x GDP per capita per QALY is applied [188]. A survey among Eastern European countries reports that the Slovak Republic has an official threshold of € 40,000. Whether this amount is explicitly applied cannot be validly inferred because only the abstract of this publication with limited information on the methods is available [160]. Garcia-Mochon et al. [2019] reported a threshold of 24 times the average monthly salary and 35 times the average monthly salary based on interviews conducted before 2019.

Slovenia

(vermutlich) explizite Schwellenwerte in SVN: € 25.000 bzw. 30.000 pro QALY

→ entspricht ca. 1 x BIP pro Kopf

According to a document by the Health Insurance Institute of Slovenia (Zavod za zdravstveno zavarovanje Slovenije, ZZZS) from 2013, the threshold for medicines reimbursed by ZZZS is € 25,000 per QALY [190-192]. This threshold would correspond to the current (2022) GDP per capita of € 24,082.27. The Health Council, the supreme counselling body of the Ministry of Health of the Republic of Slovenia, sets a threshold of € 30,000 per QALY [193]. In both cases, we interpret that the thresholds are explicit as the thresholds are regulated [191, 194]. However, Slovenia does not have a national guideline so far.

Spain

impliziter Schwellenwert in ESP: € 21.000 pro QALY

zuvor € 30.000 pro QALY

wissenschaftliche Publikationen schätzen ähnliche Werte

The Spanish pharmacoeconomic recommendation for hospital medicines published in November 2016 states that the current threshold is € 21,000 per QALY, which replaced the threshold of € 30,000 per QALY commonly used in the past. According to a report commissioned by the Spanish Ministry of Health and the Ministry of the Canaries, the basis for the reported threshold in the pharmacoeconomic recommendation is a report by Vallejo-Torres [2015]. The authors estimated a threshold range of € 21,000 and € 24,000 per QALY using an econometric analysis using a comprehensive database with demographic, health, socioeconomic and spending characteristics across regions. The authors recommended that a threshold range of € 20,000 to € 25,000 per QALY should be used in the Spanish national healthcare system. In a publication from 2016, Vallejo-Torres et al. [2016] re-estimated the threshold range, resulting in a range of €22,000 and 25,000 per QALY.

A health economic study on palivizumab for respiratory syncytial virus infection prophylaxis in preterm infants submitted in February 2017 also reports that a threshold of € 30,000 per QALY is commonly accepted in Spain [196]. In Spain, the Ministry of Health also provides a guideline for the economic evaluation of pharmaceuticals but does not report on a threshold [197].

Schwellenwert wird in ges.ök. LL nicht erwähnt

Sweden

In Sweden, there are various stakeholders involved in the decision-making process. Among these stakeholders are the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV), the county councils' group on new drug therapies (NLT), the National Board of Health and Welfare, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), the National Board of Health and Welfare (Socialstyrelsen), regional HTA agencies, and the Public Health Agency of Sweden. The involvement of various stakeholders in Sweden has accordingly resulted in several pharmacoeconomic guidelines [198-200]. Although the SBU provides an HTA guideline, the only governmental agency with an official and mandatory guideline for performing an economic evaluation is the TLV [199, 201].

Einbeziehung verschiedener Interessengruppen in Entscheidungsprozess in SWE → mehrere ges.ök. LL vorhanden

aber nur LL der Dental & Pharmaceutical Benefits Agency rechtlich bindend

According to Zhang and Garau [2020], Sweden has an implicit threshold of SEK 500,000 (€ 47,038) per QALY. This threshold is used as a "rule of thumb" in the Swedish policy debate and is no official threshold [202]. The HTA guideline by the SBU states that past TLV's subsidy (reimbursement) decisions are also used to estimate empirical threshold values for reimbursement decisions [198]. However, the real impact of this approach on decisions is unclear.

impliziter Schwellenwert in SWE: € 47.038 pro QALY

→ „Rule of Thumb"

The National Board of Health and Welfare categorise an ICER as low if SEK <100,000 (€ 9,408), moderate if SEK 100,000-499,999 (€ 9,408-47,038), high if SEK 500,000-1,000,000 (€ 47,038-94,077) or very high if >SEK 1,000,000 (€ 94,077) [200]. Svensson et al. [2015] estimated a threshold range of SEK 700,000-1,220,000 (€ 65,854-114,774) per QALY using a regression analysis (RA). Another publication estimated the marginal cost of a life year via time series and panel data approaches resulting in a k-threshold of SEK 370,000 (€ 39,000) for the year 2019 [203].

National Board of Health & Welfare schlägt ein (nicht-bindendes) Schwellenwert-Schema vor

Thailand

According to Zhang and Garau [2020], Isaranuwatchai et al. [2022], Nimdet and Ngorsuraches [2017], and Teerawattananon et al. [2014], Thailand has an explicit threshold, which is also mentioned in the Health Intervention and Technology Assessment Program's (HITAP) guideline. However, the guideline was not publicly available to check the validity. The threshold is THB 160,000 (€ 4,341), which is also "relatively close" [37] to the country's current GDP per capita of € 5,964 [1, 139].

expliziter Schwellenwert in Thailand: € 4.341 pro QALY

→ ~1 x BIP pro Kopf

[37] Relatively close, because ~€ 1,600 (€ 5,964-4,341) is almost 30% of the GDP per capita in Thailand.

USA

kein formaler HTA-Prozess in den USA

In the USA, several organisations conduct HEE. However, there is no formal HTA process like in the UK or Germany, and no "official" HTA institution informs public decision makers on reimbursement decisions. Therefore, the US does not have an explicit threshold value; instead, multiple implicit thresholds are applied. Two of the pharmacoeconomic organisations that provide health-economic guidance are the Institute for Clinical and Economic Review (US-ICER), a nonprofit organisation, and the Academy of Managed Care Pharmacy (AMCP), a professional organization representing the interest of pharmacists.

multiple, implizite Schwellenwerte durch verschiedene HTA-Institutionen

entscheidungsrelevante Schwellenwert-Range: € 47.483-142.450 pro QALY

According to some publications, the decision-relevant threshold range for most new drugs is USD 50,000-150,000 (€ 47,483-142,450) per QALY [204, 205]. This threshold range is also recommended by the US-ICER [206]. Furthermore, the economic modelling team at the US-ICER conducted a long-term cost-effectiveness threshold analysis. They estimated that the intervention costs or prices lie within the commonly cited threshold range of USD 50,000 to USD 200,000 (€ 47,483-142,450) per QALY or equal value of life years gained (evLYG). The evLYG analysis accounts for improvements in patients' quality of life while counting any gains in length of life equally regardless of the quality of life [206, p. 40]).

4.2 Countries with Modifiers

4.2.1 General Information on Modifiers

in der Praxis Kriterien wie Krankheitslast & Gerechtigkeitsaspekte, neben Effizienzüberlegungen auch entscheidungsrelevant

→ sog. Modifikatoren

As explained in Chapter 3, HEEs aim to inform decision and policy makers of the efficient use of resources in the healthcare system by minimising costs and maximising health outcomes [3, 4]. The baseline thresholds described in the previous sections give an orientation up to which ICER a new intervention would contribute to maximising health. However, as outlined in Chapter 3.5, health maximisation and efficiency are not the only aims of decision and policy makers and may also not reflect societal preferences on resource allocation. Other reimbursement criteria (often called modifiers), such as equity or severity of disease, can be considered in different forms in the reimbursement process: either in a quantitative form by altering the ICER or the threshold or by applying criteria or weighing during the deliberation process. The latter is usually done in a qualitative form (see Chapter 3.5).

quant. Modifikatoren erhöhen den entscheidungsrelevanten Schwellenwert oder ändern die ICER

The idea behind quantitative modifiers is that the health gains of specific populations or specific health care interventions should be valued differently in monetary terms. If modifiers are applied to thresholds, they usually increase the ICER threshold levels. Quantitative modifiers are directly applied in the HEE, where they have an impact on the recommendation and conclusion. However, the use of quantitative modifiers in the HEE or thresholds is usually based on directives from decision or policy makers.

qual. Modifikatoren modifizieren die Entscheidung nachdem bereits ges.ök. Evidenz generiert wurde

Qualitative modifiers or so-called decision-modifying criteria are decision criteria that are intended to supplement purely health economic and efficiency considerations in the decision-making process [1]. In contrast to quantitative modifiers, which are already taken into account in the calculations of the HEE, qualitative modifiers enter the decision-making or appraisal process after (an unmodified) health economic evidence has been generated.

Each modifier or criterion, such as disease severity, can be a quantitative modifier altering the ICER or threshold or a qualitative modifier affecting the reimbursement decision. Notably, some kind of criteria are always applied in decision-making. However, these criteria are not always made explicit and transparent. In this section, we present modifiers which are used explicitly in the countries of interest.

Kriterien wie bspw. Krankheitslast können sowohl quant. als auch qual. sein

In the following, we describe which of the modifying practices are applied. We follow the presentation format of the results as in Zhang and Garau [2020] and accordingly provide an updated overview of the modifiers frequently used in different jurisdictions. Table A-2 in the Appendix provides the full extracted information of the identified literature.

Präsentation & Analyse der Modifikatoren gemäß Zhang & Garau [2020]; vollständige Infos in Tabellen im Appendix

4.2.2 Overview of Modifiers

Countries with Modifiers

In total, 15 of the 24 (62.5%) countries use modifiers that either alter the ICER or threshold in the health economic evaluation or affect the final reimbursement decision. Twelve countries use quantitative modifiers that increase the ICER threshold or the ICER in the HEE. The Czech Republic and England and Wales are the countries that apply also ICER modifying approaches for disease severity instead of threshold modifying approaches. Six countries have officially stated qualitative modifiers that supplement efficiency considerations in the decision-making process. Three of the 15 jurisdictions (Canada, Czech Republic, England and Wales) have quantitative and qualitative modifiers in place. Table 4-5 gives an overview of the countries with modifiers and the type of modifiers.

15 der 24 Länder wenden Modifikatoren an (12 Länder mit quant. & 6 Länder mit qual. Modifikatoren)

3 Länder haben quant. & qual. Modifikatoren: CAN, CZE & E&W

Table 4-5: Overview of countries with modifiers and type of modifier

Country	ICER or Threshold modifiers (quantitative modifiers)	Decision modifiers (qualitative modifiers)
Australia		X
Canada	X	X
Czech Republic	X	X
England and Wales	X	X
Hungary	X	
Ireland	X	
Japan	X	
Netherlands	X	
Norway	X	
Scotland		X
South Korea		X
Slovak Republic	X	
Sweden	X	
Thailand		X
United States of America	X	
∑ 15 countries	**∑ 12 countries with quantitative modifiers**	**∑ 6 countries with qualitative modifiers**

Abbreviations: ICER … Incremental Cost-Effectiveness Ratio

Modification Criteria

Identified guidelines and publications mention several different modifying criteria. In total, ten types of modifying criteria were identified:

- Severity of disease including end-of-life treatments.
- Rare diseases (orphan disease).
- Equity.
- Specific indications and diseases (e.g. non-orphan diseases in oncology, paediatric indications).
- Availability of therapeutic alternatives/unmet needs.
- Budget impact.
- Uncertainty of ICER/Overall confidence in the effect.
- Innovation factor.
- High-impact single and short-term therapies (SSTs).
- Public health relevance.

Quantitative modifiers are applied for four criteria: Severity of disease, rare diseases, specific indications and diseases, and SSTs. Qualitative modifiers are deployed for almost all modifying criteria except for specific indications and diseases and SSTs. Table 4-6 gives an overview of the distribution of the modifying criteria and the type of modifier each country has. The most often used modification criteria are severity of disease and rare disease (both, applied as quantitative threshold modifiers and qualitative decision modifiers), followed by equity considerations, specific indications and diseases and availability of therapeutic alternatives. All other criteria are only used by single countries.

10 Modifikationskriterien:

Krankheitslast,

seltene Krankheit,

Gerechtigkeitsaspekte,

spezifische Indikation,

Verfügbarkeit von Alternativen,

Budgetfolgen,

Unsicherheit ICER/Effekt,

Innovationsfaktor,

hochwirksame Therapien,

Public Health Relevanz

quant. Modifikatoren für 4 Kriterien: Krankheitslast, seltene Krankheiten, spezifische Indikationen & hochwirksame Therapien; qual. Modifikatoren für fast alle Kriterien außer spezifische Indikationen & hochwirksame Therapien

Table 4-6: Overview of modifying criteria, countries, and type of modifier

Modifying criteria	Countries with ICER or threshold modifiers (quantitative modifiers)	Countries with decision modifiers (qualitative modifiers)	n of countries with QNM/QLM/QNM+QLM for each modifying criterion
Severity of disease (including end-of-life treatments)	Netherlands, Norway (health loss), Sweden, Czech Republic, England and Wales[38]	Australia ("Rule of rescue"), Czech Republic[39], South Korea	5/3/8
Rare diseases (Orphan diseases)	England and Wales, Hungary, Ireland, Japan, Slovak Republic, Sweden, USA	Scotland, South Korea	7/2/9
Equity	-	Australia, Canada, Thailand	0/3/3
Specific indications and diseases (non-orphan diseases)	Canada (oncology), Japan (paediatric labelling, oncology)	-	2/0/2
Availability of therapeutic alternatives/unmet needs	-	Australia, Czech Republic, England and Wales, Scotland, South Korea	0/5/5
Budget impact	-	Australia, England and Wales	0/2/2
Uncertainty of ICER/Overall confidence	-	Australia, England and Wales	0/2/2
Innovation factor	-	Czech Republic	0/1/1

[38] England and Wales: Severity of disease including end-of-life treatments and unmet need affect the decision indirectly, because the QALYs are already weighted in the HEE.

[39] Czech Republic: Severity of disease: Highly innovative drugs (HID) for severe diseases with markedly higher efficacy, greater safety, or no existing alternative treatment can apply for temporary reimbursement (TR)

Modifying criteria	Countries with ICER or threshold modifiers (quantitative modifiers)	Countries with decision modifiers (qualitative modifiers)	n of countries with QNM/QLM/QNM+QLM for each modifying criterion
High-Impact single and short-term therapies (SSTs)	USA	-	1/0/1
Public health relevance	-	Australia	0/1/1
Σ	**Σ 11 countries**	**Σ 7 countries**	

Abbreviations: n … Number, QNM … Quantitative Modifier, QLM … Qualitative Modifier

Severity of Disease

Krankheitslast: quant. Modifikator in E&W, CZE, NL, NOR & SWE

qual. Modifikator in AUS, CZE & KOR

The Netherlands, Norway, Australia, the Czech Republic, England and Wales, Sweden, and South Korea define disease severity as a modifying criterion. The Netherlands, Norway, and Sweden use disease severity as a threshold modifier leading to an upward adjustment of the thresholds directly in the HEE. The Czech Republic and England and Wales also adjust the ICER itself for severe diseases. Australia, the Czech Republic, England and Wales, and South Korea use disease severity as a criterion that has implications on the decision-making process in a qualitative way on top of the health economic evidence.

ICER or Threshold-Modifying

NL: 3 verschiedene Schwellenwerte für 3 Krankheitslast-Intervalle

Krankheitslast per "Proportional Shortfall"

In the Netherlands, the severity of disease is defined as disease burden. The disease burden according to WHO's Global Burden of Disease serves as a determinant for three threshold levels [174, 207]. The disease burden intervals for the three threshold levels are quantified with the proportional shortfall (PS) method. The PS approach considers the fraction of QALYs that people lose relative to their remaining life expectancy instead of the absolute QALYs gain or loss [1, 208-213].

Krankheitslast-Intervalle:

The following three disease burden intervals and thresholds apply:

- With a disease burden of 0.1 to 0.4, a threshold of € 20,000 per QALY is applied. **0,1-0,4: € 20.000 (Baseline-Schwellenwert)**
- A disease burden of 0.41 to 0.7 results in a threshold of € 50,000 per QALY. **0,41-0,7: € 50.000**
- In case the disease burden lies between 0.71 and 1.0 the applied threshold is € 80,000 per QALY. **0,71-1: € 80.000**

NOR: "Health-Loss"-Kriterium spiegelt Grad der Krankheitslast wider

„Health-Loss" in QALYs wird durch "Absolute-Shortfall"-Ansatz berechnet

6 Krankheitslast-Klassen & Schwellenwerte

In Norway, three criteria are crucial for systematic priority setting in the healthcare system: the health-benefit criterion, the resource criterion, and the health-loss criterion, the latter reflecting disease severity. However, according to the pharmacoeconomic guidelines, only the health-loss criterion should have an impact on the threshold [176, 177]. Health-losses are calculated by the absolute shortfall (AS) approach. The absolute shortfall is defined as the absolute reduction in future healthy life years for people with the disease compared to what people of the same age but without the disease can expect [177]. Based on this approach, the Magnussen Working Group recommended six severity classes (0 to 0.39, 4 to 7.9, 8 to 11.9, 12 to 15.9, 16 to 19.9, and >20 QALY; NOK 275,000 per QALY (€ 25,871), NOK 385,000 per QALY (€ 36,219), NOK 495,000 per QALY (€ 46,568), NOK 605,000 per QALY (€ 56,916), NOK 715,000 per QALY (€ 67,265), and NOK 825,000 per QALY (€ 77,613)) [209]. This modified threshold range corresponds to a range of € 24,746-98,984 The group proposed and reported that some aspects of severity may not be captured by the AS approach [214].

SWE: Erstattung in Zusammenhang mit Krankheitslast gesetzlich geregelt → modifizierter Schwellenwert: € 188.496 pro QALY

Swedish law states that only disease severity and cost-effectiveness should be considered for reimbursement decisions [202]. However, the identified higher threshold value of SEK 2,000,000 (€ 188,496) per QALY (based on information from an interview in Zhang and Garau [2020]) seems to apply for reimbursement decisions in the context on rare diseases. Whether this threshold also applies to the severity of disease is therefore not clear.

CZE: Krankheitslast beeinflusst Schwellenwert nicht direkt, aber die ICER

The Czech Pharmacoeconomic Society states that the social consequences of the disease and its impact on family and carers should be accounted for by adopting a societal perspective in the HEE, as in Sweden or Norway. Accounting for these additional criteria could reflect the social consequences of certain diseases (paediatric patients, patients with a disease causing significant disability). These considerations of social consequences affect the benefits and costs in the HEE and, thus, the ICER, respectively but they do not directly affect the ICER threshold.

Krankheitslast beeinflusst Schwellenwerte indirekt per QALY-Gewichtung

In England and Wales, disease severity is considered by QALY weighting in the HEE. This practice affects the ICER at first and only indirectly alters the finally accepted ICER threshold, because theoretically the adjusted ICER could be below the usually accepted ICER threshold. Diagnostics are ruled out from this criterion [1, 158].

QALY-Gewichtung auch bei End-of-Life-Therapien

For end-of-life therapies, the NICE introduced an additional guidance [215]. The guidance allowed the Appraisal Committee to give additional weight to additional QALYs at the end-of-life, if three criteria are met [215, 216]:

- The treatment is indicated for patients with a short life expectancy (≤24 months).
- There is sufficient evidence indicating that the treatment provides an extension to life (≥additional 3 months) compared to current NHS treatments.
- The treatment is licensed or otherwise indicated, for small patient populations.

zusätzliche QALY-Gewichtung bestimmt Kosten-Effektivität

If these three conditions are met, the Appraisal Committee will consider …

- The effect of giving greater weight to QALYs gained during terminal illness stages, assuming that patients experience the extended survival time with the same QoL as a healthy person of comparable age.
- How much extra weight would need to be given to the QALY benefits for this patient group in order for the cost-effectiveness of the technology to fall within the current acceptable cost-effectiveness threshold range.

mittlerweile gibt es einen "inoffiziellen" Schwellenwert für End-of-Life-Therapien

This provision enables end-of-life technologies to receive NHS approval even when their cost-effectiveness ratios exceed NICE's standard threshold of £ 20,000 to £ 30,000 (€ 23,453-35,180) per QALY. Initially, the application of the QALY weights in the end-of-life context was similar to the application for disease severity, meaning that the weights affect the ICER and only indirectly alters the accepted ICER threshold [216, 217]. However, from time to time, the maximum value of £ 50,000 (€ 47,483.38) per QALY resulting from the reimbursement of end-of-life therapies above the baseline thresholds has become the de facto standard threshold for end-of-life interventions in practice [215-217].

Decision-Modifying

The Australian submission guideline mentions the modifier disease severity in the rule of rescue and unmet needs [1, 143, 218]. The Czech Republic uses a two-tier reimbursement system. One tier is for the permanent reimbursement of medicinal products, and the other process is for temporary reimbursement (TR) for a 2- to 3-year period. Highly innovative drugs (HID) in the context of severe diseases with markedly higher efficacy, greater safety, or no existing alternative treatment can apply for temporary reimbursement [1, 219, 220]. The Czech Pharmacoeconomic Society proposes that other criteria should be evaluated in rare or highly rare disease areas (orphan diseases), in cases of unmet need, or in situations where the relationship between surrogate clinical outcomes and hard outcomes is not well studied or detectable. It is unclear to what extent these criteria are considered in SÚKL's assessment and decision-making process [156]. In South Korea, the severity of disease applies as a modifier in the case of cancer and diseases in the terminal stage (end-of-life).

AUS: Krankheitslast als Teil des Kriteriums „Rule of Rescue" wird in ges.ök. LL erwähnt & hat Einfluss im Entscheidungsprozess

CZE: zweistufiges Erstattungssystem → vorübergehende Erstattung für Medikamente im Kontext schwerer Erkrankung

KOR: Berücksichtigung im Krebs- & End-of-Life-Kontext

Rare Diseases (Orphan Diseases)

Interventions indicated for orphan or rare diseases have a special status in the reimbursement process in nine jurisdictions. An upward adjusted threshold is used in England and Wales, Hungary, Ireland, Japan, the Slovak Republic, Sweden, and the US. In Scotland and South Korea, orphan drug designation also requires non-health economic considerations in reimbursement.

seltene Krankheiten als modifizierendes Kriterium in 9 Ländern

ICER or Threshold-Modifying

In England and Wales, the size of benefit for highly specialised technologies increases the threshold [1, 158]. Highly specialised technologies are interventions for very rare conditions in the sense of orphan diseases [158]. For incremental QALYs gained over the lifetime less than or equal to 10, the weight is 1; between 11 to 29 additional QALYs over the lifetime, the weight is between 1 and 3 (using increments of 0.1), and for QALY gains ≥ 30, the weight is 3. The baseline threshold for highly specialised technologies is £ 100,000 per QALY (€ 94,967). This results in a threshold range of £ 100,000-300,000 (€ 94,967-284,900) for highly specialised technologies.

E&W: höhere Schwellenwerte für "hochspezialisierte Technologien" (abhängig vom Effekt)

→ € 94.967-284.900 pro QALY

Hungary uses a 3 to 10 times GDP per capita threshold range for orphan drugs. This corresponds to HUF 18,227,907-60,759,689 (€ 46,584-155,280). To arrive at the specific threshold, Hungary applies a specific calculation scheme. The absolute value of the incremental discounted QALY between the technology under investigation and the comparator is relevant in the calculation. For incremental discounted QALYs above 0.5 and below 20, the threshold varies proportionally between 3 and 10 times the GDP per capita. The threshold for incremental discounted QALYs of 20 or more is ten times the GDP per capita. Generally, the Hungarian guideline recommends that in addition to the results of the health economic analysis, other aspects and domains according to the EUnetHTA Core Model should be considered when assessing health technologies [165].

HUN: BIP-basierte (3-10 x GDP) Schwellenwert-Range für „Orphan Drugs"

→ € 46.584-155.280 pro QALY

In Ireland, in the case of ultra-rare diseases, a threshold of € 100,000 is used. Definitive factors for determining this threshold amount could not be identified [1, 167].

IRL: € 100.000 pro QALY für „sehr" seltene Krankheiten

Japan applies a threshold of JPY 7,500,000 (€ 54,336) for orphan drugs. However, no information on why this specific amount is used was available.

JPN: € 54.336 pro QALY für "Orphan Drugs"

The Slovak Republic uses a threshold of 3.5 to 10 times the GDP per capita (€ 62,836-179,531) for orphan drugs including ATMPs. If a medicine loses orphan status in Slovakia, the Marketing Authorization Holder (MAH) must submit a pharmacoeconomic analysis of the drug to the Ministry of Health within 120 days. If the drug is no longer cost-effective according to the basic threshold value, it is removed from the list of medicinal products. [188, 189]

SVK: BIP-basierter Schwellenwert für "Orphan Drugs" & ATMPs

→ 3,5-10 x BIP pro Kopf pro QALY

Sweden uses a threshold of SEK 2,000,000 (€ 188,154) for orphan drugs. The information on the threshold is from an interview in Zhang and Garau [2020] and seems to apply for reimbursement decisions in the context of rare diseases. Swedish law states that only disease severity and cost-effectiveness should be considered for reimbursement decisions [202]. Why this specific amount is used could not be identified. In the US, a threshold of USD 500,000 (€ 474,834) is applied for medicines in the case of ultra-rare conditions [221].

SWE: € 188.154 pro QALY für "Orphan Drugs"

USA: € 474.834 pro QALY für Medikamente bei sehr seltenen Erkrankungen

Decision-Modifying

The designation of interventions for rare diseases is a relevant factor in the decision-making process in Scotland and South Korea. However, in which form the rare disease criterion affects reimbursement decisions is not clear from the identified documents.

"Orphan Drugs" relevant bei Erstattungsentscheidungen in SCO & KOR

Equity

Gerechtigkeitsaspekte

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE by applying equity weights.

keine quant. Modifikatoren

Decision-Modifying

Equity aspects play an exceptional role in the decision-making process in Australia, Canada, and Thailand [1, 141, 143, 147, 218]. However, the documents do not present details on how equity criteria are precisely applied. The Canadian guideline only states that equity refers to notions of fairness and can be considered in terms of health and health care. Furthermore, it refers to horizontal equity meaning that equal people should be treated equally, and vertical equity meaning that different people should be treated differently, leaving unclear how this affects decisions [1, 147].

Gerechtigkeitsaspekte spielen in AUS, CAN & THA spielen eine nennenswerte Rolle

CAN: horizontale & vertikale Gerechtigkeit

Specific information on equity aspects from official Thai documents was also not available. Three scientific publications in the context of imiglucerase for Gaucher disease in Thailand report that it was included in the benefit package on account of equity considerations even though the agent did not provide good value-for-money [139, 222, 223]. The authors mention that imiglucerase was included for equity reasons, because it treats a very rare disease and the associated HEE estimated that there would be no more than five people who require treatment per year [139, 223]. Furthermore, if imiglucerase were not publicly reimbursed, it *"would mainly be available for the rich who are able to pay for imiglucerase before undertaking bone marrow transplantation"*, which is part of the benefits package [139].

Thailand: keine spezifischen Infos zu Equity-Aspekten in offiziellen Dokumenten verfügbar

For Australia, no specific information on equity aspects was available, but only that equity plays a role in the decision making process [218].

AUS: keine genauen Infos zu Gerechtigkeitsaspekten

Specific Indications and Diseases

spezifische Indikationen

ICER or Threshold-Modifying

In Canada and Japan, oncology drug thresholds are greater than baseline thresholds for standard reimbursement decisions. Canada's threshold for cancer therapies is CAD 140,000 (€ 102,227), and Japan's threshold is JPY 7,500,000 (€ 54,336) [1, 147, 170].

CAN & JAP: höhere Schwellenwert für Onkologika (€ 102.227 bzw. 54.336 pro QALY)

In Japan, paediatric labelling as part of a drug's indication also increases the decision-relevant threshold to JPY 7,500,000 (€ 54,336).

JAP: pädiatrische Medikamente

Decision-Modifying

None of the identified countries use decision-modifiers regarding specific indications and diseases.

keine qual. Modifikatoren

Availability of Therapeutic Alternatives

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE regarding the criterion availability of therapeutic alternatives.

Verfügbarkeit therapeutischer Alternativen: keine quant. Modifikatoren

Decision-Modifying

The availability of therapeutic alternatives has an impact on the decision-making process in Scotland, South Korea, Australia, the Czech Republic, and England and Wales[40]

- Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice (Scotland) [224]
- Availability of substitutes (South Korea) [1, 185]
- No presence of effective therapeutic alternatives (Australia, Czech Republic[41]) [1, 143, 218-220]
- Unmet need (Australia, England and Wales) [1, 143, 158, 218]

Verfügbarkeit therapeutischer Alternativen relevant im Entscheidungsprozess in 5 Ländern: AUS, CZE, E&W, KOR & SCO

There is no information in the identified documents in what way these criteria precisely affect decisions.

allerdings keine genauen Infos über die konkrete Berücksichtigung im Entscheidungsprozess

Budget Impact

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE regarding the criterion budget impact.

[40] In Thailand, general equity-related aspects play a role in the decision-making process. Whether this includes availability of alternatives could not be validated from official documents (see description in the section Equity)

[41] Highly innovative drugs (HID) in the context of severe diseases with markedly higher efficacy, greater safety, or no existing alternative treatment can apply for temporary reimbursement (TR) [1, 219, 220]

Decision-Modifying

Australia considers the impact of any decision on the budget [143]. However, information on a specific limit beyond which an intervention is not reimbursed is not available. Hence, it is also not clear to what degree budget impact affects the decision.

Budgetfolgen relevant in AUS, aber genaue Infos zu Budgetlimitationen nicht verfügbar

In the case of England and Wales, the NICE and NHS have proposed doubling the Budget Impact Test (BIT) threshold to £ 40 million (€ 37,986,800), up from its current level of £ 20 million (€ 18,993,400) initially introduced in 2017. This change was outlined in a consultation document released on July 31, 2024. When a technology exceeds the BIT threshold, the NHS has the option to initiate commercial negotiations with the manufacturing company. These negotiations aim to address the financial challenges of implementing the technology, following the guidelines established in NHS's Commercial Framework for New Medicines [225]. The clinical evaluation and CEA of a technology by NICE remains independent from both the budget impact assessment and the BIT implementation [225, 226]. By doubling the BIT threshold to £ 40 million (€ 37,986,800), the policy will maintain its original purpose of identifying technologies with significant NHS budget implications. This adjustment ensures that only a small proportion of evaluated technologies will exceed the threshold, consistent with the initial BIT policy objectives. The public consultation phase of the BIT increase closed on the 25. September 2024 [225].

E&W: Erhöhung des "Budget Impact Test"-Betrags von € 18.993.400 auf 37.986.800

BIT = "Haushaltsbelastungstest" für Preisverhandlungen

Erhöhung ist aber unabhängig von CEA & Schwellenwerte

Zhang and Garau [2020] report that Canada and the Netherlands deem budget impact as an important factor in reimbursement decisions. However, this information could not be verified by the identified literature.

CAN & NL: genaue Infos zur Relevanz von Budgetfolgenkriterium unklar

Uncertainty

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE regarding the criterion uncertainty.

Unsicherheit: keine quant. Modifikatoren

Decision-Modifying

In the case of Australia, England and Wales, the uncertainty of the ICER and overall confidence in the effect plays a role in the decision-making process [1, 143, 158, 218]. For example, if the most plausible ICER of a new therapy is beyond £ 20,000 (€ 23,453) or £ 100,000 (€ 94,967) per QALY for highly specialised technologies, decision makers in England and Wales will consider the degree of certainty and uncertainty around the ICER and aspects that relate to uncaptured benefits and non-health factors [158]. Greater thresholds are used in the case of certainty of the ICER. In the case of recommendations with managed access pertaining highly specialised technologies, the committee can make a recommendation for further evidence to be generated if there is still significant resolvable uncertainty present [158]. How exactly the consideration of uncertainty is operationalised by the decision-making committee is unclear.

AUS & E&W: Unsicherheit der CEA/CUA-Ergebnisse & Effekte werden im Entscheidungsprozess berücksichtigt

Operationalisierung aber unklar

Innovation Factor

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE regarding the criterion innovation factor.

Innovationsfaktor: keine quant. Modifikatoren

Decision-Modifying

In the Czech Republic, for highly innovative drugs (HID) manufacturers do not need to prove cost-effectiveness for reimbursement. HID are granted a temporary reimbursement for a maximum of 3 years. However, no specific definition of the term HID was available. The two-tier reimbursement system already mentioned only specifies that for temporary reimbursement, a HID needs to have a markedly higher efficacy, greater safety, or no existing alternative treatment.

CZE: "Highly Innovative Drugs" → vorübergehende Erstattung (max. 3 Jahre)

High-Impact Single and Short-Term Therapies (SSTs)

ICER or Threshold-Modifying

In the USA, a threshold of USD 150,000 (€ 142,450) is applied for high-impact and short-term therapies (SSTs). The US-ICER defines SSTs as follows:

> *"SSTs are defined as therapies that are delivered through a single intervention or a short-term course (less than one year) of treatment that offer a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes. SSTs include potential cures that can eradicate a disease or condition and high-impact therapies that can produce sustained major health gains or halt the progression of significant illnesses."* – Institute for Clinical and Economic Review (ICER) [2020, p. 12].

The high-impact SSTs criterion is unique to the US context and could not clearly be assigned to another modifier criterion.

hochwirksame & kurzfristige Therapien (SSTs): US-spezifischer Modifikator

Definition SSTs: Einzelinterventionen & kurzfristige Therapien (<1 Jahr) mit großen Gesundheits- bzw. Heilungspotential

Decision-Modifying

None of the identified countries use decision-modifiers regarding high-impact SSTs.

keine qual. Modifikatoren

Public Health Relevance

ICER or Threshold-Modifying

None of the identified countries adjust the ICER or threshold of the HEE regarding the criterion public health relevance.

Public-Health-Relevanz: keine quant. Modifikatoren

Decision-Modifying

In Australia, public health issues such as development of resistance (for antimicrobial agents) also influence PBAC decision-making. Submissions need to include relevant data about the development of resistance, if the development or potential development of resistance has been demonstrated to affect health outcomes [218].

AUS: Resistenzen spielen eine Rolle im Entscheidungsprozess

5 Economic Evaluation and Thresholds in Austria

5.1 Legal References to Efficiency and Economic Evaluation

We identified several laws, including a reference to efficiency (*Wirtschaftlichkeit*) or explicitly addressing economic evaluations. The list of laws outlined below is not claimed to be exhaustive but is intended to provide examples of the legal points of reference for health economic evaluations and thresholds in Austria.

Rechtstexte im AT Gesundheitssystem mit Bezug auf „Wirtschaftlichkeit"

Allgemeines Sozialversicherungsgessetz (ASVG) (General Social Insurance Act)

The ASVG [227] regulates the responsibility for social insurance, including health insurance, in Austria. A key reference to efficiency occurs in the so-called economic efficiency requirement (*Wirtschaftlichkeitsgebot*) in § 133, which states: „The medical treatment must be sufficient and appropriate but must not exceed what is necessary." *["Die Krankenbehandlung muss ausreichend und zweckmäßig sein, sie darf jedoch das Maß des Notwendigen nicht überschreiten."]*. The terms "sufficient", "appropriate" and "not exceeding what is necessary" have their origin in §182 (2) of the German "Reich Insurance Code" *(Reichsversicherungsordnung, RVO)* and were adopted from there [228].

Allgemeines Sozialversicherungsgesetz (ASVG): ***„Krankenbehandlung ausreichend & zweckmäßig, darf jedoch das Maß des Notwendigen nicht überschreiten"***

A specific regulation exists for assessing pharmaceuticals to be included in the positive list of reimbursable drugs in the outpatient sector (§ 351g ASVG/ VO-EKO). The term economic efficiency (*Wirtschaftlichkeit*) occurs in several paragraphs but primarily relates to price or cost comparisons between the drug under evaluation and alternatives.

Wirtschaftlichkeit im Kontext von Erstattungen von Medikamenten für niedergelassenen Bereich erwähnt

Notably, the law summarises price and cost comparisons and pharmacoeconomic studies under the umbrella term "health economic evaluation" *[gesundheitsökonomische Evaluation]*. Therefore, the term "health economic evaluation" has a different and broader meaning in the law than the definition of economic evaluation within HTA and, thus, within our report.

entsprechendes Gesetz verwendet Begriff „ges.ök. Evaluation" in breiterer Bedeutung

Paragraph (§) 25 of the rules of procedures ("VO-EKO") refers more precisely to the international standard concept of HEE, yet using the term "pharmacoeconomic studies" [229]. The rules of procedure outline that economic evaluations are required in two types of submissions for reimbursement: a) if the manufacturer claims that the drug offers a substantial additional benefit compared to existing drug treatment alternatives for all or a subgroup of patients for whom the drug is licensed for; and b) if the drug is submitted for listing in the "yellow box" of the code of reimbursement (*Erstattungskodex, EKO*) and there are no alternative drug treatment options already listed [229]. Efficiency needs to be demonstrated in the form of a cost-benefit ratio[42]. *[e.g., „Bei der Fallgruppe nach § 24 Abs. 2 Z 5 und 6 ist von der Wirtschaftlichkeit auszugehen, wenn deren Abgabe … gesundheitsökonomisch sinnvoll und vertretbar ist, insbesondere im Hinblick auf das zu erwartende Kosten/Nutzenverhältnis für die definierte Gruppe von Patienten/Patientinnen (§ 351c Abs. 9 Z 2 ASVG). Dies ist vom an-*

§ 25 VO-EKO bezieht sich auf HEE, wie sie in diesem Bericht definiert sind

[42] The term cost-benefit ratio is used as a general term for cost-effectiveness and is not restricted to cost-benefit analysis as described in Chapter 3.2.3

tragstellenden Unternehmen anhand einer pharmakoökonomischen Studie nachzuweisen. Der Dachverband kann bei Offensichtlichkeit auf die Vorlage der pharmakoökonomischen Studie durch das antragstellende Unternehmen vorläufig verzichten."].

Krankenanstalten und Kuranstaltengesetz (KAKuG) (Federal Hospitals Act)

Krankenanstalten & Kuranstaltengesetz (KAKuG) §19 (4): Zweckmäßigkeit & Wirtschaftlichkeit muss bedacht werden

The KAKuG [230] regulates hospital care. In § 19 (4) of the KAKuG (4), efficiency is addressed concerning guidelines issued by hospital Pharmaceutical and therapeutic committees (PTC) (*Arzneimittelkommission)* addressing procurement and handling of pharmaceuticals. *[„Bei der Erarbeitung von Richtlinien über die Beschaffung und den Umgang mit Arzneimitteln ist … auch auf die Zweckmäßigkeit und Wirtschaftlichkeit Bedacht zu nehmen."]*.

KAKuG §62e (4): Wirtschaftlichkeit im Zusammenhang mit teuren & spezialisierten Arzneimitteln

In §62e (4) of the KAKuG, economic efficiency is stated in context with assessing selected high-cost or specialized drugs to be provided in hospitals or at the interface between inpatient and outpatient care. The law states that an appraisal board must formulate recommendations for using these drugs. It further states that these recommendations need to include the assessment of the added medical-therapeutic benefit based on a comparison with therapeutic alternatives in conjunction with 'economic efficiency' (according to predefined criteria) and possible application criteria *["Die Beurteilung des medizinisch-therapeutischen Zusatznutzens auf Basis eines Vergleichs mit therapeutischen Alternativen in Zusammenschau mit der Wirtschaftlichkeit (nach vorab definierten Wirtschaftlichkeitskriterien) und möglichen Anwendungskriterien."]*. Notably, the German term 'Wirtschaftlichkeit' does not necessarily have the same meaning as the English term 'cost-effectiveness' but may also cover affordability, indicated by the budget impact. According to the wording of the rules of procedure, affordability seems to be an explicit element of 'economic efficiency', next to cost-effectiveness (§ 11(3): *"Jedenfalls zu berücksichtigen sind der zu erwartende Budget Impact sowie die Vergleichbarkeit des Preises im Kontext des internationalen Preisgefüges."*).

Referenz zu Kosten-Effektivität UND Leistbarkeit (budget impact)

Hersteller müssen ges.ök Informationen bereitstellen

In § 62e (6), the law further states that the manufacturer is obliged to provide the appraisal board with the information required to prepare the recommendations, naming economic evaluation and the example of cost-utility analysis as one of the requested sources.

KAKuG referenziert auf die europäische HTA-Verordnung

Contrary to the ASVG, the KAKuG uses the term "Health Technology Assessment" and refers to the European HTA regulation when describing the evaluation of pharmaceuticals [230].

Bundesgesetz zur Qualität von Gesundheitsleistungen (Federal Act on the Quality of Health Care)

Effizienz im Bundesgesetz zur Qualität von Gesundheitsleistungen: *„Verhältnis zwischen dem Einsatz & dem Ergebnis einer Leistung nach dem Wirtschaftlichkeitsprinzip unter Berücksichtigung der Kostendämpfung"*

The Federal Act on the Quality of Health Services [231] uses the term "efficiency" and defines it as the relationship between input and result while additionally referring to the economic principle (*Wirtschaftlichkeitsprinzip*) used in other laws. *[„Effizienz: Verhältnis zwischen dem Einsatz und dem Ergebnis einer Leistung nach dem Wirtschaftlichkeitsprinzip unter Berücksichtigung der Kostendämpfung."]*. Efficiency is mentioned as a goal of quality work *["Qualitätsarbeit hat einen wesentlichen Beitrag zur mittel- bis langfristigen Steigerung der Effektivität und Effizienz im Gesundheitswesen zu leisten …"]*. It is further mentioned in the context of federal quality guidelines or regulations which need to take into account efficiency among other parameters *[… "wobei auf Folgendes zu achten ist: Stand der Wissenschaft und der Erfahrung bezüglich der Effektivität und der Effizienz"]*.

15a B-VG (Bundesverfassungsgesetz) Zielsteuerung-Gesundheit (Federal Target-Based Health Care Act)

15a B-VG Zielsteuerung-Gesundheit: effizienter Mitteleinsatz & bessere Koordinierung von Gesundheitsleistungen

This federal constitution act uses the term "efficiency" when referring to the responsibility for using taxes and contributions provided by the population [232]. *[„Die Verantwortung für den Einsatz der von der Bevölkerung bereitgestellten Steuern und Beiträgen verlangt nach Instrumenten zur Steigerung der Effektivität und Effizienz der Gesundheitsversorgung"]* [232]. Furthermore, the law outlines several principles to increase efficiency, such as putting a greater focus on health promotion and prevention or better coordination of services at the state level. *["Erhöhung der Effektivität und Effizienz … durch die Bündelung komplexer Leistungen an geeigneten Standorten und die Nutzung der im KAKuG und im ÖSG vorgesehenen Möglichkeiten"]* [232].

Bundesfinanzgesetz (Federal Budget Act)

Bundesfinanzgesetz: *"… Wirtschaftlichkeit in der Gesundheitsversorgung für die Zukunft nachhaltig sicher(zu)stellen"*

The health Chapter of the Federal Budget Act [233] refers to the economic principle in the context of objective one, which outlines that „*economic* efficiency *[Wirtschaftlichkeit]* has to be considered among other principles (quality, effectiveness) in the interest of citizens and patients to sustain health care *[„Im Interesse der Bürger:innen bzw. Patient:innen sind die Qualität, die Wirksamkeit und die Wirtschaftlichkeit in der Gesundheitsversorgung für die Zukunft nachhaltig sicherzustellen"]*.

5.2 Health System Characteristics and Current Use of Economic Evaluation

AT: sozialversicherungsbasiertes Gesundheitssystem

Gesundheitssystem ist stark fragmentiert

Austria has a social security-based health care system; therefore, it can be classified as a Bismarck system according to the typology outlined in 2.4. However, in addition to social security contributions, which funds 44 % of health care expenditure, taxes and private sources (out-of-pocket payments), with a share of 30 % and 26 %, respectively, play an important role [234]. The overall health care spending in 2022 was € 49.9 billion, representing 11.2 % of the gross domestic product [235]. The system is highly fragmented in terms of governance and service provision. The health insurance is responsible for outpatient services (including the use of pharmaceuticals), while responsibility for hospitals (both hospital inpatient and outpatient settings) is mainly at the regional governance level. Responsibilities of preventive activities differ according to prevention type. Some rest within the federal government (e.g. vaccines), and others are within the health insurance (e.g., certain screening programmes), but funding may be shared between all of them (Figure 5-1).

Abbildung 5-1 bietet eine Übersicht der Zuständigkeiten & Prozesse im AT Gesundheitssystem; Anwendung von HEE kein Standard in AT → nur in Ausnahmefällen

Figure 5-1 presents an overview of the different processes for coverage decisions. It shows that separate processes exist for pharmaceuticals and non-pharmaceuticals, and within pharmaceuticals, processes are different between drugs paid for by the health insurance for the outpatient sector and drugs used in hospitals. As explained in 5.1, within the processes shown, formal requirements to use economic evaluations (as defined in international standards) currently exist for outpatient pharmaceuticals; however, only for the specified cases described. The manufacturer must submit the studies as part of the dossier in these cases.

HEE-Einreichungsleitfaden für Hersteller listet notwendige Daten & Infos

In the submission manual for EKO reimbursement applications, basic reporting requirements for economic evaluations are outlined (title; research question; perspective; alternatives analysed; type of economic evaluation; source of data used; quantitative results of patient benefits and costs; quantification of costs disaggregated by type of cost, quantities and prices as well as direct and indirect costs; discounting; sensitivity analysis; summary of results) [229].

Leitfaden enthält keine ges.ök.-methodischen Anforderungen;

However, the manual does not specify methodological requirements, except for the types of costs that need to be considered (direct costs related to services paid by the health insurance, hospital costs, medical rehabilitation) and costs to be excluded (out-of-pocket payments).

Ausnahme: zu berücksichtigende Kostenarten

While methodological issues have partly been addressed in a consensus document initiated by a private industry consulting company [236], to date no formal guideline specifying methodological details exists.

bis heute existiert keine formale ges.ök. Leitlinie in Österreich

Compared to many international guidelines, the document does not provide precise methodological guidance and leaves room for flexibility (e.g. concerning the outcome parameter used, the methods of sensitivity analysis applied etc.) [237]. Its use is not mandatory and rather meant as a recommendation.

österreich. HTA-Handbuch hat keinen rechtsverbindlichen Charakter

Another document with methodological content is the Austrian HTA manual [30]. It summarises methods from international guidelines and presents state-of-the-art textbook methods without specifying the method in cases where alternative approaches are possible (e.g., using CUA or CEA). It, therefore, also has a recommendation but no mandatory character.

tatsächliche Verwendung von HEE im Entscheidungsprozess unklar

Little is known about the actual use of the submitted HEE in the appraisal processes and the role their results play in the recommendations made by the drug evaluation committee *(Heilmittelevaluierungskommission, HEK)*. According to a report on drug reimbursement in Austria, so far, methods that may be applied for critically assessing the HEE and summarising the study results for the drug evaluation committee have not been published [232]. The reports for the drug evaluation committee and the recommendations the committee makes are both confidential.

zudem keine „offiziellen" Dokumente zur Relevanz ges.ök. Evidenz im SV- Kontext

A study from 2006 demonstrated that in almost all cases where HEE studies were part of the dossier, their use in decision-making was rather restricted because of the limited relevance and credibility of the study [238]. This analysis is almost 20 years old, and the situation may have changed since then. However, in the absence of publicly available descriptions on how HEEs inform decisions, the significance of HEE-study results and the role of ICERs as a decision criterion are unclear.

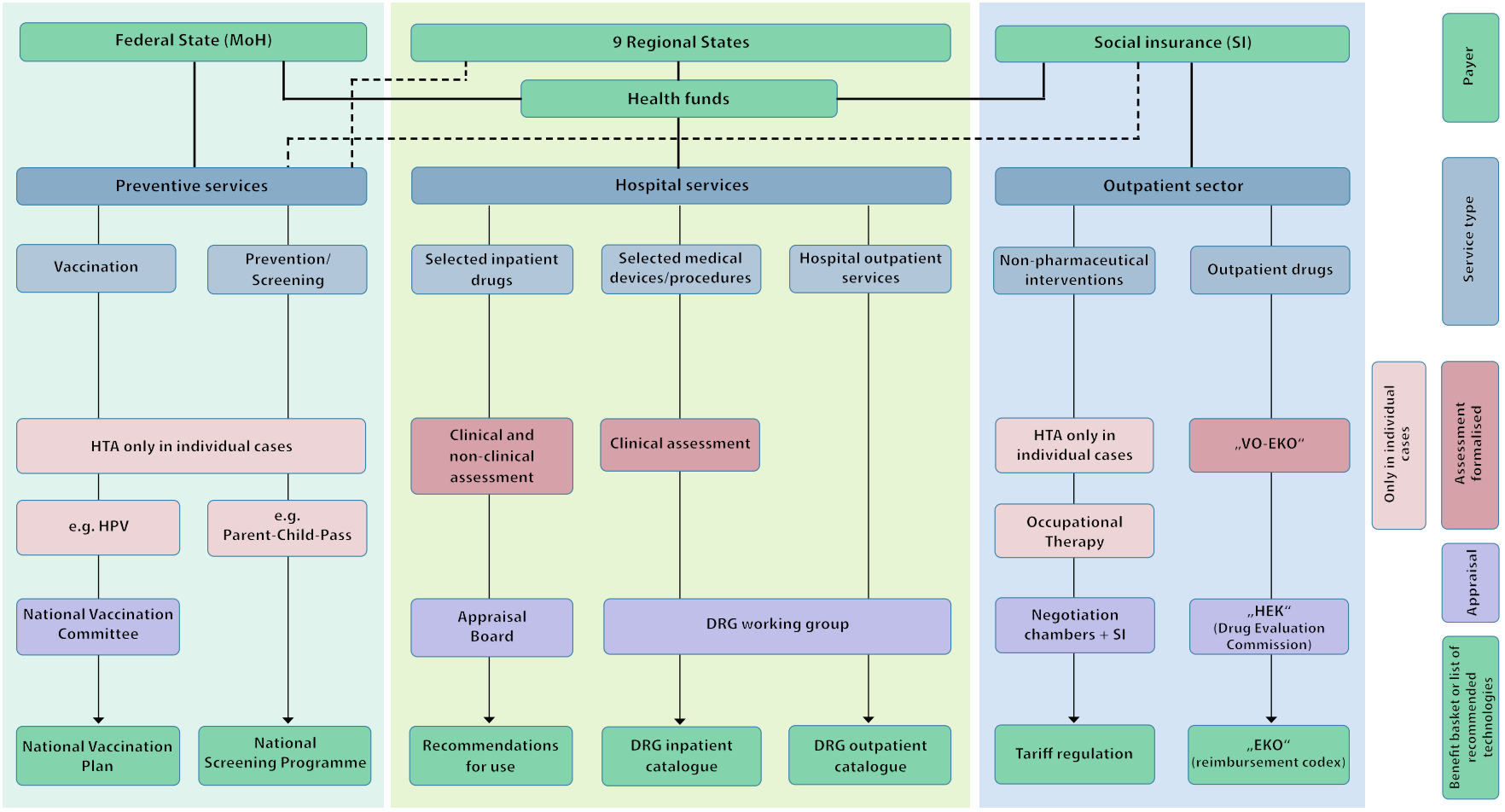
neues Gesetz (2024) zur Bewertung „teurer" Arzneimittel („Bewertungsboard") bietet Möglichkeit, HEE von Herstellern anzufordern

In addition to reimbursement of pharmaceuticals in the outpatient sector, a recently passed law addresses the evaluation of selected high-cost or specialised drugs used in hospitals or at the interface between hospitals and outpatient care. The law states that the industry can be requested to provide an economic study, mentioning cost-utility analysis as an example. The law and the according rules of procedure do not outline further details on the methods to be used and what role the study results play in the reimbursement decisions of the products. Still, these are likely to be more detailed in upcoming implementing regulations and method manuals [230].

HEE haben in allen anderen Prozessen in AT keine formale Rolle (Prozesse in Abbildung 5-1)

In all other processes described in Figure 5-1, economic evaluation has no formal role and may only be used in single cases in an ad hoc manner. For none of the cases, a cost-effectiveness threshold exists in Austria and the concept of a threshold has also not been discussed so far.

Responsibilities, processes and benefit catalogues in the Austrian health care system



[1] *Efficiency frontier analysis (EFA): EFA gives no explicit ICER threshold but a price ceiling. Therefore, modifications apply only partly for EFA.*

Abbreviations: DRG … Diagnostic Related Groups, HPV … Humane Papillomviren, VO-EKO … Rules of Procedures Code of Reimbursement/Verfahrensordnung Erstattungskodex

Figure 5-1: Responsibilities, processes, and benefit catalogues in the Austrian healthcare system

5.3 Options for Implementing Economic Evaluation and Thresholds in Decision-Making

Figure 5-2 outlines a decision algorithm for using economic evaluations in combination or without thresholds that we defined according to the information presented in Chapters 3 to 4. The first question that needs to be answered is whether economic evaluation should generally play a formal role in reimbursement decisions. In other words, whether cost-effectiveness should be an explicit decision criterion. Notably, deciding against using cost-effectiveness evidence means that decisions will be made without systematic assessment of whether paying for a new technology represents an efficient use of resources. If this information is regarded as important, cost-effectiveness evidence needs to be generated and used more systematically following high-quality methodological standards.

Abbildung 5-2: Entscheidungsalgorithmus über Anwendung von HEE

Effizienz ein ausdrückliches Entscheidungskriterium?

falls ja, …

Deciding to use cost-effectiveness evidence more systematically requires further decisions to be made in the following four domains:

→ zu berücksichtigende Faktoren:

- Type of economic evaluation to be used (CBA or CEA/CUA)
- In the case of CEA/CUA: using it with or without a threshold
- In the case of threshold: which method should be used to define the threshold?
- In both cases: should criteria be introduced to modify the ICER or the threshold or should this be left to the deliberative process in the appraisal committees?

HEE-Typ: CEA, CUA, CBA,

mit/ohne Schwellenwert,

Kalkulationsmethode,

Modifikatoren

All options presented have different advantages and disadvantages. A summary of these is presented in Table 5-1.

Implementing a more standardised and explicit use of CEA/CUA in decision-making requires several preparatory activities, which many countries using economic evaluations as part of HTA have already completed:

Maßnahmen bevor Implementierung von HEE in AT:

- Preparing a guideline outlining the details of the method to be applied by manufacturers or other bodies commissioned to do CEA/CUA for decision support (perspective to be used, discount rate, type of sensitivity analysis …)
- Defining a method to calculate unit costs and establishing a unit cost library
- For CUA: eliciting HRQoL measures (utility weights) in the Austrian population (e.g., EQ-5D)
- Defining tools for critical appraisal for studies submitted by manufacturers
- Defining methods for critical appraisal of models/programme codes
- Training of staff in HTA units involved in critical appraisal
- Training of decision makers (basic understanding of methods, interpretation of results)

Ausarbeitung einer ges.ök. (Methoden)Leitlinie,

Einheitskosten(katalog),

HRQoL-Messwerte für die österreich. Population,

Methoden zur kritischen Bewertung von Studien & ges.ök. Modellen,

Schulung von Personal in HTA-Instituten & Entscheidungsträgern

If a decision pro threshold is made, according to the system characteristics, the lived reality regarding health care spending, and the legal basis, Austria belongs to the countries with a flexible budget setting. Therefore, a fixed threshold will have to be defined taking into account the pros and cons listed in Table 5-1.

österreich. System- & Budgetkontext muss berücksichtigt werden

Table 5-1: Overview of further decisions to be made when applying health economic evaluations

	Domains	Pro	Con
Type of health economic evaluation	**CEA including CCA**	■ CEA enables to achieve a specific (clinical) health objective within a disease class ■ CCA captures complexity of complex interventions	■ CEA restricts itself to disease-specific clinical outcomes ■ CCA: prone to subjective interpretation
	CUA	■ CUA (and, to a lesser extent, CEA) are standard HTA methods in other countries (a lot of international experience available) ■ CUA using QALYs as an outcome measure enables comparison across disease areas and indications and is a standard approach in most countries	■ QALYs have been discussed as being potentially inappropriate for some diseases (e.g., mental illness) and for conceptual limitations but would then be used across all disease areas ■ Other utility measures less established ■ To be used according to scientific standards, substantial preparatory work is required (e.g., population HRQoL weights)
	CBA	■ Does not require to calculate ICER thresholds, because results show net benefit in monetary units ■ Easy to interpret (straight forward) results ■ CBA intention is to operationalise the opportunity cost approach in a "highly stylised" (theoretical) form according to Neoclassical economic theory/welfarism ■ CBA enables policy makers to compare policy interventions and allocate resources across policy areas (social care, justice, or the healthcare sector)	■ CBA is based on Neoclassical economic theory/Welfarism: Highly stylised theoretical conceptualisation that accepts the welfarist paradigm (see Chapter 3.1.3 on Efficiency, Utilitarianism, Welfarism, and Extra-Welfarism) ■ Challenging to operationalise: Methods to define costs and benefits in monetary units complex, time-consuming, and discussed controversially ■ Not used as a standard method within HTA in any other country ■ Results may oversimplify the complexity as it still requires value judgements for health benefits
Using a CEA or CUA in combination with a threshold	**Threshold available**	■ Explicit recognition of opportunity cost ■ Allows straightforward interpretation of ICER and orientation on whether a new technology represents efficient resource use ■ Supports consistency and transparency of decision-making ■ Provides arguments for price negotiations	■ Manufacturers may set the price so that ICER matches the threshold (over-pricing of products)[43] ■ Some types of thresholds require substantial effort to be calculated properly ■ A threshold is considered to put an explicit number on the value of a life
	Threshold not available	■ No resources are required to define a threshold ■ Leaves more room for price negotiations (but less negotiation power)	■ Interpretation of ICERs difficult ■ May lead to higher inconsistency in decisions
Method used to define a threshold	**Empirical method**	■ Aggregated expenditure and outcome data (mortality, life expectancy) is easily available compared to complete data on reimbursed and not reimbursed interventions, but gives only a proxy of opportunity cost ■ Some empirical concepts incorporate the direct relationship between the threshold and health care budget	■ For most approaches full information and transparency on past decisions, including compared interventions, costs, and benefits, are required ■ Estimation of the threshold using aggregated data may bias the threshold results (reverse causality, confounding) ■ Empirical ICER threshold in a flexible budget setting may not reflect the opportunity cost
	GDP approach	■ Easy to calculate/requires little effort	■ Can lead to inappropriately high thresholds ■ The link between economic productivity and willingness to pay for health has been discussed controversially

[43] Even if the threshold is not made explicit as in many countries, manufacturers can infer the value of the threshold from retrospectively analysing decisions.

	Domains	Pro	Con
Method used to define a threshold *(continuation)*	**Societal WTP**	■ Reflects the societal preferences and values of the relevant population groups in relation to health gains ■ Different societal WTP thresholds or a range for different populations or indications can be calculated	■ Requires effort to elicit societal WTP in a sound way ■ If society's preference or valuation of health changes, the WTP needs to be reevaluated ■ A range of societal WTP thresholds may lead to inconsistencies instead of a universal threshold
	Efficiency frontier approach (EFA)	■ Efficiency frontier can be calculated for the efficient combination of currently available interventions in a specific therapeutic area ■ EFA follows a strict rule regarding the cost or expenditure increase proportionally to a health improvement (proportional rule)	■ EFA gives no explicit threshold, but a price ceiling is calculated by using the proportional rule. ■ Focus on a specific therapeutic area is at odds with textbook (health) economics, because it may lead to inefficient use of healthcare budgets → Raising thresholds for specific diseases diverts resources from more cost-effective treatments elsewhere, potentially reducing overall health benefits across the healthcare system.
Modification	**Modification of ICER**	■ Increases transparency by including modifiers in a formalised way	■ Weights need to be defined; some methods (eliciting from a representative population sample) requires substantial research resources ■ Methods to define weights are discussed controversially (premature; pseudo-objectivity)
	Modification of threshold	■ Increases transparency by including modifiers in a formalised way	■ Creating a separate series of cost-effectiveness thresholds is seen as premature by some method experts (methods to weight QALYs are not reliable enough) [239]
	No quantitative modification of ICER or threshold but using modifiers in the appraisal process	■ Does not require quantitative data on weights and qualitative modifiers (e.g., severity of disease, orphan drugs, availability of therapy alternatives etc.)	■ Difficult to apply consistently and unbiased in the absence of a formalised process ■ May lead to high cognitive load ■ Transparent only if criteria used are included in the justification for reimbursement or use of a technology

Abbreviations: CBA … Cost-Benefit-Analysis, CCA … Cost-Consequences-Analysis, CEA … Cost-Effectiveness Analysis, CUA … Cost-Utility-Analysis, EFA … Efficiency Frontier Approach, GDP … Gross Domestic Product, HRQoL … Health Related Quality of Life, HTA … Health Technology Assessment, ICER … Incremental Cost-Effectiveness Ratio, QALY … Quality-Adjusted Life Years, WTP … Willingness-to-Pay

If weighing of ICERs or introducing modifiers for thresholds is implemented, another set of activities is required.

- Defining which criteria are relevant (severity of disease, rarity …).
- Eliciting societal preferences on different equity issues.
- Deciding which method to use for quantifying.

Überlegungen zu (quant.) Schwellenwert- & ICER-Modifikatoren: Kriterien? öffentliche Präferenzen? Quantifizierung?

If, instead of modifying the ICER or threshold, it is preferred that modification and weighing of different reimbursement criteria be done during the deliberative process by an appraisal committee, decision criteria and a transparent process (decision rules, documentation etc.) must be defined. Otherwise, there is a risk that the process becomes unstructured and opaque. The literature provides practical guidance on how to set up such transparent evidence-informed deliberative processes [135, 240, 241].

Überlegungen zu (qual.) entscheidungsrelevanten Modifikatoren: transparente Dokumentation & Entscheidungsregeln

HEE and thresholds are highly sensitive topics that policy makers hesitate to address. As the experience with introducing the new process to evaluate selected hospital drugs systematically demonstrated, any initiatives linking the provision of interventions or reimbursement to more standardised criteria and harmonising access are often immediately interpreted as cost-containment measures, restricting access or are criticised for withholding highly innovative measures from patients.

Standardisierung von Entscheidungsprozessen & Effizienzaspekte werden oft missverstanden

It is to be expected that moving towards using HEE more extensively in Austria will be controversially discussed among stakeholders, with resistance from specific stakeholder groups (e.g., patient advocates, doctors, and some political parties). Some of the likely oppositions stem from the widespread view that access to health care is seen as a right which should not be denied for financial reasons, without being aware of the consequences such an attitude has for financing health care and people's own income (e.g., increasing health insurance contributions) [242].

Implementierung von ges.ök. Methoden wird voraussichtlich kontrovers diskutiert werden

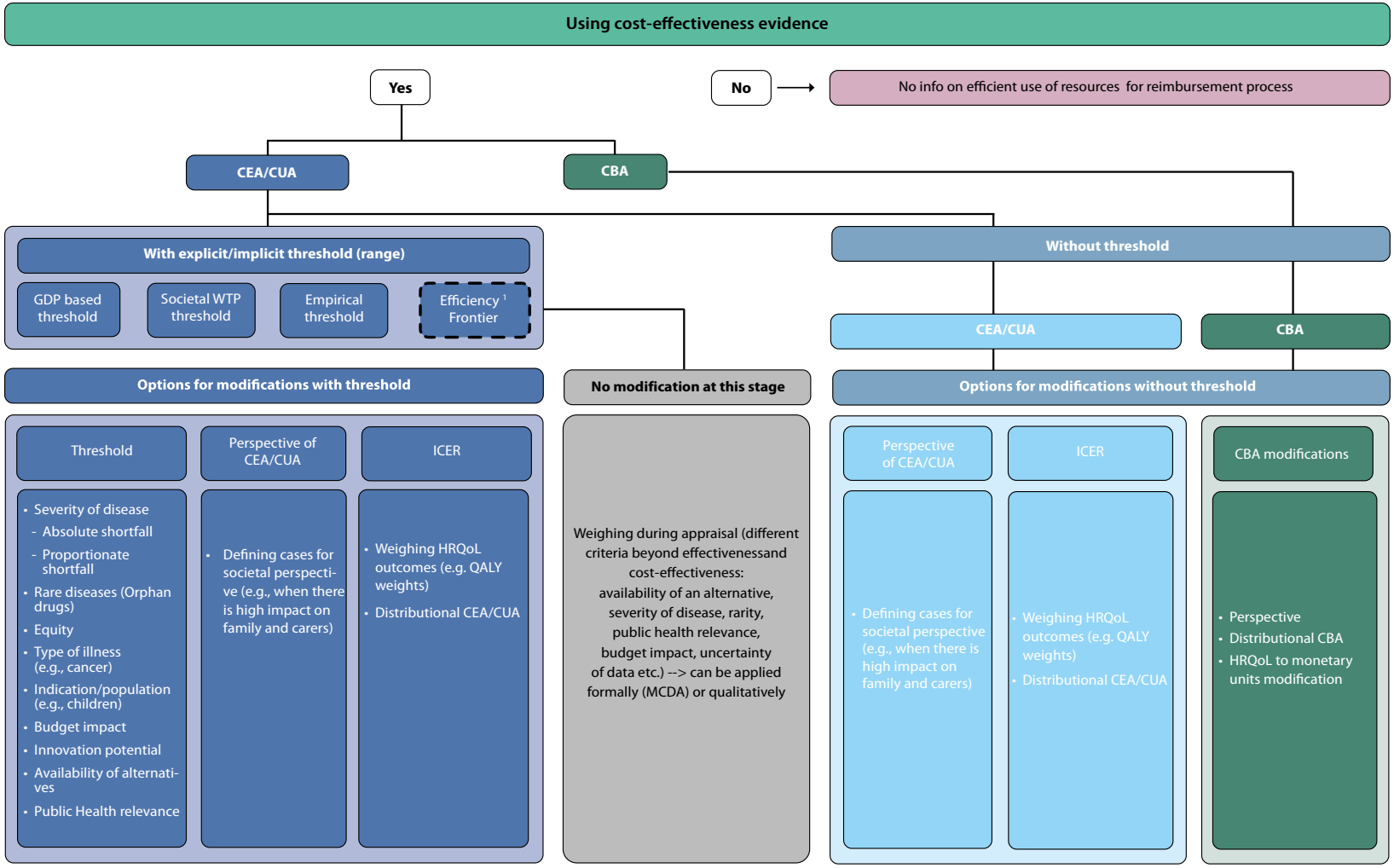
Other concerns have their roots in wrong assumptions and a lack of knowledge on what HEE and thresholds are and the advantages and limitations of using or not using them in decision-making. If HEE is to be used more actively and transparently, it is therefore recommended that an awareness-raising strategy be developed proactively, informing about the changes and the implementation plan and combating myths. For example, to explain in an understandable way the difference between cost containment (rationing) and using resources efficiently (rationalising). It is also essential to make clear that resource allocation decisions are made every day, even without applying HEE, and that non-transparent decisions make it difficult to identify whether they lead to the discrimination of particular patients or patient groups.

Aufklärungsarbeit & öffentliche Informationen können Missverständnisse vermeiden

bspw. Rationalisierung ≠ Rationierung

Another relevant task is to commission a legal opinion by lawyers and to align the terms used in the legal documents with the scientific methodological terms (e.g., using the term economic evaluation only for the study types presented in 0) to have a common and mutually understandable language.

Rechtsgutachten inkl. sprachliche Anpassung an internationale Standardbegriffe



[1] *Efficiency frontier analysis (EFA): EFA gives no explicit ICER threshold but a price ceiling. Therefore, modifications apply only partly for EFA.*

Abbreviations: CBA … Cost-Benefit-Analysis, CCA … Cost-Consequences-Analysis, CEA … Cost-Effectiveness Analysis, CUA … Cost-Utility-Analysis, GDP … Gross Domestic Product, HRQoL … Health Related Quality of Life, HTA … Health Technology Assessment, ICER … Incremental Cost-Effectiveness Ratio, MCDA … Multi-Criteria Decision-Analysis, QALY … Quality-Adjusted Life Years, WTP … Willingness-to-Pay

Figure 5-2: Decision algorithm for using economic evaluations in combination with or without thresholds

6 Summary and Critical Reflection

6.1 Efficiency Considerations in Decision-Making and ICER Thresholds

(implizite) Priorisierung immer Teil von Ressourcenallokation

Effizienz ist eines von vielen Priorisierungskriterien

→ ICER-Schwellenwert

Decisions on the allocation of resources for competing purposes always involve prioritisation. One criterion that decision or policy makers can use for prioritisation of temporarily scarce resources is the efficiency criterion (Chapter 3.1). The efficient resource use for alternative actions, such as different health care interventions, can be exemplified by different types of economic evaluations, each of which has advantages and disadvantages (Chapters 3.2 and 5.3). A specific reference value – the so-called ICER threshold – gives decision and policy makers a reference point for whether the use of resources is efficient and whether the intervention represents "value for money" (Chapter 3.3).

Schwellenwert = zusätzlicher Ressourceninput, den man bereit ist, pro zusätzlichen Output aufzugeben

→ Opp.-Kosten = "reale" Ressourcenkosten

On the one hand, the ICER threshold represents the additional resources one is willing to temporarily give up per additional unit of health effect (e.g. QALYs). On the other, this figure reflects the "opportunity cost" – one of the central concepts of economic thinking. Personnel or resources used for one specific need are temporarily no longer available for other purposes in the economy. Hence, opportunity cost is the "price" of real resources that a decision or policy maker pays to provide a specific health care intervention instead of using the resources for alternative purposes. Opportunity cost comprises all relevant resources an intervention consumes, not just the costs affecting the available financial budget or expenditures. Economic cost also values resources and components of interventions for which no market prices are available, or no price has been paid.

"wahre" Opp.-Kosten meist nicht darstellbar

theoretische Annahmen treffen in der Realität nicht zu, bspw. ist das Gesundheitsbudget (meist) nicht beschränkt → flexibles Budget

However, true opportunity cost cannot be observed because the underlying assumptions derived from neoclassical economic theory are never satisfied in reality (Chapter 3.3.3) [49]. First and foremost, an assumption that is often violated is that the healthcare budget is fixed. Some jurisdictions may have fiscal rules (e.g. "Schuldenbremse" in Germany, EU convergence criteria) that give them less leeway for public spending more general which can have an impact on the flexibility of the healthcare budget. Others may have an annual fixed healthcare budget in place (e.g., the annual budget of the British NHS defined by parliament). Yet often, the healthcare budget may still be exceeded for a given budget year, leading to a flexible budget setting. Others have generally a more flexible budget. The decision as to whether a budget should be fixed or flexible is a political one.

Budgetflexibilität (Budgettyp) hat Auswirkungen auf die Schwellenwert-Logik:

fixes Budget → variabler Schwellenwert

variables Budget → fixer Schwellenwert

The flexibility of budgets has conceptual implications for the ICER threshold. We showed that a flexible financial budget to fund necessary resources is required if the ICER threshold is an exogenously fixed value. If the budget and resources are fixed, the ICER threshold conceptionally results from maximising health outcomes within the fixed budget. In this case it is no choice variable and evolves over time. However, in practice, this principle, which would require permanent adaptions of thresholds, is not strictly followed for practicability and feasibility reasons. As Cleemput et al. [2008] put it, the ICER threshold value is usually viewed as a fixed value, thereby neglecting the difference between fixed and flexible budget settings.

Yet, for specifying an ICER in a country, the distinction of ICER thresholds according to the budget-setting seems more helpful than that between supply and demand side [11, 98, 111] (Chapter 3.3).

Unterscheidung Schwellenwert nach Budgettyp & nicht angebots- & nachfrageseitige

6.2 Methods to Specify ICER Thresholds for the Relevant Decision-Making Context

If a decision or policy maker decides to use a threshold as a decisive criterion for reimbursement decisions, an approach to defining an ICER threshold must be chosen (Chapter 3.3.4). Due to methodological challenges to approximating the actual opportunity cost, several ways to estimate ICER thresholds exist in the health economic literature. The essence of each approach and its similarities and differences are not easy to disentangle. Generally, methodological research on thresholds has received far less attention than how to calculate the ICER and the methods of HEE in general. As Brouwer et al. [2019] put it:

welchen methodischen Ansatz zur Kalkulation eines Schwellenwerts?

→ weitere methodische Forschung notwendig

> *"One could say, we have become better and better in producing estimates of incremental cost-effectiveness of new technologies, but still have fairly little idea about what to compare these figures to."*

Again, the budget setting has implications for the appropriate method to define a threshold. Within the empirical methods to define an ICER threshold, approaches for a fixed and flexible budget setting exist. Empirical ICER threshold approaches in a fixed budget setting are labelled as "true" opportunity cost approaches by some authors [11, 98] (Chapter 3.4.1.). One of the most influential attempts to estimate an empirical ICER in a fixed budget setting in the sense of average displacement of health is an econometric analysis by a research group around Claxton et al. [2015]. They estimated a threshold of £ 12,936 per QALY, which is far below the current fixed threshold range of £ 20,000 to 30,000 (€ 23,453-35,180) per QALY applied by NICE.

vorliegender Budgettyp beeinflusst Schwellenwert-Kalkulation & Anwendung

fixes Budget & empirisch geschätzter Schwellenwert = „wahre" Opp.-Kosten

However, the DHSC in the UK uses the estimate by Claxton et al. [2015] as a basis for their cost per QALY "at the margin" (marginal product of health) of £ 15,000 (€ 17,590) in their impact assessments [98, 159]. The estimate and the proposed marginal product of health is an *"expression of how many QALYs are gained (or lost) if funds are added to (or taken from) the NHS budget"* [159, 243]. This interpretation of opportunity cost corresponds to the average displacement of health within a fixed budget as mentioned in Chapter 3.4.1 on Empirical ICER Thresholds in a Fixed Budget Setting: Opportunity Cost Threshold Approach. The DHSC and the authors state that their approach differs from the ICER threshold considered by NICE: *"Whilst the two are not dissimilar concepts, they are distinct from one another and should not be considered interchangeable"* [243]. The main distinctive characteristic (fixed vs. flexible budget threshold/opportunity cost) has been outlined in the report in Chapter 3.3.3 The ICER Threshold.

→ Gesundheits- & Sozialministerium in UK verwendet in Folgenabschätzungen einen Schwellenwert von € 17.590

(Annahme: fixes Budget)

One application of the empirical ICER threshold approach in a flexible budget setting can be found in the publication by Pichon-Riviere et al. [2023]. The estimated thresholds are based health expenditure and life expectancy data that are generally available macro-level data. To arrive at a country-specific threshold, it is only necessary to specify the evolution of health spending and life expectancy increases in which they expect to remain in a given period.

fixer empirischer Schwellenwert & flexibles Budget …

The threshold value is then calculated based on these two variables. However, the approach has a few drawbacks such as reverse causality and confounding due to the simplicity of the model. Therefore, whether these types of empirical thresholds reflect the health opportunity cost is disputable.

… Ansätze in diesem Kontext haben Limitationen: Confounding & Retrokausalität

Empirical ICER thresholds have stringent evidence requirements, regardless of the budget setting. The feasibility depends on the data availability of past reimbursement, expenditure, and health outcome data. The more accurately the estimated threshold should correspond to the opportunity cost, the less aggregated the data can be [11].

unabhängig von Budget haben empirische Schwellenwerte strenge Evidenzvoraussetzungen

There are three further options for defining efficiency reference points within a flexible budget setting: the GDP-based approach, the societal WTP approach and the efficiency frontier approach, whereby the last one gives a price ceiling and no explicit threshold.

3 weitere methodische Ansätze in einem flexiblen Budgetsetting:

ICER thresholds based on a country's per-capita GDP were the most commonly cited thresholds [123, 124] (Chapter 3.4.2.). The reason for using the GDP-based threshold, such as the WHO-CHOICE [126], is that GDP is, on the one hand, a proxy for lost earnings due to illness and, on the other hand, a proxy for the ability to "resource" an intervention. Although critics argue that the WHO's GDP-based ICER thresholds are too high compared to ICER thresholds elicited by other methods, they are still widely used. One reason for the use may be that GDP-based thresholds are relatively easy to calculate [9].

1) BIP-basiert bzw. "WHO-Ansatz":

BIP ist ein Proxy für die „Zahlungsfähigkeit"

wird allgemein als zu hoch angesehen

The societal WTP threshold for an additional health gain, such as QALY, is the amount of budget funds or resources society is temporarily willing to give up from somewhere else to obtain the additional health gain [12]. Within this approach, it is possible to incorporate population preferences, such as equity considerations and aspects beyond the mere valuation of health. However, eliciting all relevant societal preferences in a robust and comprehensive way is currently methodologically challenging, if not impossible. Therefore, studies calculating thresholds using weights dependent on societal preferences are rare and often done within methodological research rather than applied in the decision-making practice. Another criticism is that societal WTP thresholds do not represent "true" opportunity cost [11, 98].

2) „soziale Zahlungsbereitschaft":

Einbindung von sozialen Präferenzen möglich

hat aber auch Limitationen: robuste Schätzung/Aggregation von Präferenzen

In the EFA, the most efficient combination of currently available interventions forms an efficiency frontier (3.4.4). A new intervention is embedded within this efficiency frontier, and a potential price ceiling can be calculated using the proportional rule. The needed resources are only constrained by the potential health improvements. However, a downside is that no social preferences are considered.

3) Effizienzgrenze: Preisobergrenze, aber keine sozialen Präferenzen berücksichtigt

Regardless of the approach, the aim of all methods is to maximise health outcomes within a population. Decision and policy makers need to be aware of the differences between each approach and its implications – especially regarding whether the right approach is used given the budget setting.

Ziel aller 3 Ansätze: Maximierung der Gesundheit, aber alle Ansätze mit Limitationen verbunden

6.3 The Application of Thresholds and Modifiers in Practice

Anwendung von Schwellenwerten variiert stark zwischen Ländern

The country overview showed that the application of ICER thresholds varies significantly across identified jurisdictions (Chapter 4.1.1). Almost all identified countries are high-income countries (HICs) by GDP, except for China and Thailand. Whether this indicates that efficiency criteria have higher priority or resources are more limited in HICs compared to low- and middle-income countries (LMICs) cannot be determined. LMICs may still apply reference values that are not publicly communicated. Furthermore, LMICs may be more resource-constrained, leading decision and policy makers to apply efficiency criteria more stringently. Potential causes for the different degrees of resource scarcity and inclination for applying efficiency criteria need further exploration, including institutional (post-colonial) structures, higher medicine prices, non-sovereign monetary policy, and dependency on the world market [244, 245].

fast alle identifizierten Länder mit hohem Einkommen

weitere Forschung zu Anwendung von Effizienzkriterien notwendig

50 % der Länder mit Schwellenwert geben keine zugrundeliegende Methode an

Strikingly, 50% of the identified jurisdictions with thresholds do not specify an underlying method to calculate them. Thus, these jurisdictions either arbitrarily specify their threshold without a theoretical or empirical foundation or they do not communicate the method. Almost half of all the jurisdictions have a baseline threshold range and not a single baseline threshold value. The specific reasons for the use of a range are not clear. A range might give decision-makers more leeway in the decision-making process. However, this comes at the cost of consistency, especially if the range is wide.

50 % haben Schwellenwert-Range

9 Länder trotz Kritik an WHO-Ansatz mit BIP-basiertem Schwellenwert; kein Land mit Schwellenwert basierend auf sozialer Zahlungsbereitschaft

A significant number of jurisdictions (9 countries) use a GDP-based threshold, although the literature challenges this approach as it tends to give a too high threshold. Only a minority of jurisdictions use an empirical ICER threshold. This may be because calculating an accurate empirical threshold goes hand in hand with high evidence requirements regarding the needed data. While some countries have elicited societal WTP threshold values as part of academic research, none use them in decision-making practice.

hohe Variation in (nicht-PPP-adjustierten) Schwellenwerten

The threshold level shows a high dispersion across countries. The baseline threshold values range between € 4,000 and € 50,000. Jurisdictions with a Bismarck system have the lowest ICER threshold (median) (chapter 4.1.2). However, all systems' mean, and median threshold range is between € 25,000 and € 30,000 per QALY.

umgekehrt U-förmiger Verlauf zwischen HLE & Schwellenwerten & Schwellenwert-Typ hat möglicherweise Einfluss auf Schwellenwerthöhe

The relation between HLE and the applied thresholds shows a reverse U-shaped pattern. One interpretation is that the effect of the threshold on HLE is positive until it reaches a maximum and decreases when the threshold is further increased. If thresholds are separated by their defined method, a different relationship between HLE and threshold for each method type arises. This observation may indicate that the type of threshold has an impact on the variation of the threshold. However, one must be cautious with interpreting these results. Life expectancy depends on further factors, and the relationship can be the other way round, i.e. higher HLE leads to higher thresholds (reverse causality). Therefore, no in-depth inferential tests were conducted. Whether all the interpretations are valid needs a more in-depth investigation.

vorsichtige Interpretation der Zusammenhänge & weitere wissenschaftliche Analysen notwendig

BIP pro Kopf hat nur bedingt Einfluss auf Schwellenwerthöhe …

Although one might expect that the threshold correlates with the GDP per capita, even in cases where other methods are used to define it, the GDP per capita could only partly explain the threshold level in our analysis. Hence, it may be the case that countries with high income do not have a higher thresh-

old compared to countries with a lower income. As with the relation of HLE and thresholds, other covariates may explain more of the threshold variation across jurisdictions. Country-specific characteristics such as age distribution of the population, burden of disease, budget for healthcare, societal values, or socio-economic factors may play a role. These factors may be more influential in higher-income countries that do not have an underlying method to determine the threshold.

… andere länderspezifische Erklärungsvariablen möglicherweise mehr Erklärungspotential

The analysis of modifiers showed that decision-making in many jurisdictions explicitly involves more criteria than a pure efficiency assessment (Chapter 4.2). While quantitative modifiers are directly applied in the HEE, where they impact the ICER or ICER threshold, qualitative modifiers or so-called decision-modifying criteria are applied during the deliberative decision-making process. Criteria considered most often are disease severity or rarity, but others, such as equity or innovation, also exist. We identified 12 countries that use threshold and ICER modifiers, whereby the types of criteria considered and the methods to quantify modified ICERs or thresholds are heterogeneous across jurisdictions. Decision-making modifiers could only be identified for a few countries (six of the 24). However, it is often unclear how these are considered or what weight is given to them in the decision-making process. We do not know whether other countries do not apply modifiers for decision-making, or jurisdictions just do not make this transparent. The latter seems more likely than the former.

Nicht-Effizienz-Aspekte fließen in einigen Ländern in Entscheidungen mit ein:

→ 15 der 24 Länder wenden Modifikatoren an (12 Länder mit quant. & 6 Länder mit qual. Modifikatoren)

oft unklar, wie qual. Modifikatoren im Entscheidungsprozess berücksichtigt werden

A potential issue of ICER thresholds regardless of the calculation method is that knowledge of the threshold can lead to strategic (pricing) behaviour by pharmaceutical and medical technology companies, i.e. to price interventions close to the threshold. The publicly available information on the threshold increases the companies' bargaining power. This tendency is called "threshold pricing" or "pricing to the threshold" [246, 247]. This situation reflects a strategic game between manufacturers and payers, where the threshold becomes less about efficiency and more about strategic pricing[44].

Existenz eines Schwellenwerts kann zu „Threshold Pricing" durch Unternehmen führen

Companies set the price to maximise profits by using the revealed threshold information in the following manner [246, 249]:

- Manufacturers analyse the known thresholds in their target markets.
- Conditional on the thresholds, companies determine the profit-maximising price they can charge while still maintaining "cost-effectiveness".
- If their product shows substantial clinical benefit, a manufacturer may either …
  - set prices near the upper limit of what would be considered "cost-effective", or …
  - strategically set an initial price that results in an ICER above the specified threshold. This approach anticipates subsequent price negotiations with payers, during which the price is expected to be reduced until the ICER aligns with the threshold [246].

„Threshold Pricing":

Analyse der Schwellenwerte

setzen des profit-optimalen Preis basierend auf Schwellenwert

2 Preisstrategien:

profit-optimaler Preis = Schwellenwert oder …

… initialer Preis in Verhandlung wird hoch angesetzt

[44] In decision and game theoretic terms, this strategic behaviour is called backward induction [248]. Companies start with the end goal (meeting the threshold), work backwards through decision nodes, and optimise their price point based on this analysis.

Schwellenwert als Preistreiber & Umkehrung des ursprünglichen Effizienzgedankens

This turns HEE from its feet on its head: Rather than using price as an input to determine cost-effectiveness, companies use cost-effectiveness (the threshold) as an input to determine prices. This practice compromises the fundamental aim of cost-effectiveness analysis and thresholds, which were designed to establish efficiency. Instead, meeting the threshold has become an inevitable outcome rather than a meaningful measure. As a result, prices are artificially inflated since companies price to the maximum acceptable threshold rather than basing prices on actual costs (e.g., cost-based pricing) [247, 250].

unbeabsichtigte negative Folgen transparenter Schwellenwerte, u. a. Preisabsprachen

There are some arguments that ICER thresholds are irrelevant or should not be made explicit (kept confidential), because the knowledge of the threshold increases the bargaining power of the companies or may have other adverse consequences [247, 251, 252]. A study by Brekke et al. [2023] analysed a sequential pricing model between an existing drug manufacturer and a potential new market entrant. The authors found that ICER thresholds can produce unintended negative consequences for healthcare payers and patients. Their analysis demonstrated that stricter thresholds might cause the existing manufacturer to shift strategy from accepting market entry to actively preventing it, thereby limiting patient access to new medicines. The researchers also showed that regardless of whether market entry occurs, stricter thresholds never enhance competition and may facilitate price collusion between manufacturers. According to their findings, in scenarios where an existing monopolist faces therapeutic alternatives, thresholds only prove beneficial to healthcare budgets if they result in entry deterrence. In such cases, the authors concluded that the required price reduction by the existing manufacturer to prevent competition exceeds the health losses experienced by patients who cannot access the new medicine [253].

Modifikatoren gegen "Threshold Pricing"

We showed that multiple criteria, such as the presented modifiers, or a threshold range may be used in addition to the efficiency criterion for reimbursement decisions to circumvent “threshold pricing” (see Chapter 4.2.2 Overview of Modifiers).

weitere Modifikatoren (nicht-identifiziert)

Other relevant modifiers not identified in the search could comprise the following:

- **Family and carer burden:** Patient care is often provided through unpaid work by those in their immediate environment. This burden on family members and carers can be reduced through effective therapy. Reducing the burden on family members and carers may increase willingness to pay [254].

  Familienbelastung & informelle Pflege

- **Indirect cost implications:** Certain therapies may reduce or generate indirect costs, such as through the prevention or cause of hospital admissions. When these indirect cost implications cannot be directly incorporated into pricing calculations, they can serve as additional factors influencing willingness to pay. Cost savings increase willingness to pay, whilst additional costs decrease it [254].

  indirekte Kosteneffekte

- **Environmental impact:** The healthcare system contributes to environmental degradation, which affects public health and the broader societal responsibility for sustainable healthcare delivery. Practical implementation of considering environmental impact faces challenges, including the need for standardised environmental impact measures, monetisation of environmental effects, and decisions about scope and time horizons [255].

  Umweltauswirkungen & Nachhaltigkeit

- **Distributional aspects:** Distributional aspects are more specific than the equity criterion. The rationale stems from health equity concerns,

  Verteilungsgerechtigkeit

> social justice considerations, and the recognition that equal health gains may have different social values depending on who receives them. Challenges for implementing distributional aspects include quantifying equity impacts, societal agreement on equity weights, and integrating distributional concerns with efficiency objectives. Various methods exist, from equity-weighted QALYs to differential ICER thresholds for different populations, reflecting the growing importance of addressing health inequalities in resource allocation decisions [48].

zudem kein wissenschaftlicher Konsens, wie, welche & ob Modifikatoren & Kriterien berücksichtigt werden sollen

Although threshold and modifiers are used in the health economic research practice and in decision-making, there is no scientific consensus on the correct method, and some researchers reject the quantification of another set of thresholds based on modifying criteria. The US-ICER states that it is *"premature to seek to create a separate series of cost-effectiveness thresholds related to severity, burden of illness, or need"* [256]. Arguments for such methods are that they increase consistency and transparency and reduce the cognitive load for appraisal committee members who must consider many criteria simultaneously [44, 82, 135-137, 157].

6.4 Implications for Austria

mehrere Rechtsakte im. Gesundheitssystem erwähnen Aspekte zur "Wirtschaftlichkeit", aber bisher spielten HEE nur eine untergeordnete Rolle

Anwendung von HEE kann Effizienz der Ressourcennutzung, Transparenz & Angemessenheit der Entscheidungen sicherstellen

Although several legal acts related to the healthcare system specify that efficient resource use is mandated, the systematic and transparent application of HEE and ICER thresholds have so far played minor roles in healthcare decision-making in Austria (Chapters 5.1 and 5.2) [15]. Efficiency is introduced as a general term but rarely operationalised in more detail. If the term economic evaluation appears in the law, it does not necessarily refer to the study types described under 3.2 in this report. Consequently, information on whether paying for new technologies might be an efficient use of resources is either unavailable or not explicitly discussed in the appraisal processes. Yet, every reimbursement decision implicitly affects the allocation and distribution of resources, thus addressing efficiency. As decision-makers are increasingly urged to organise fair, legitimate processes in health benefit package design, the reasonableness of decisions as perceived by stakeholders becomes more relevant [135]. The benefit of using HEE is not only to increase the efficiency of resource use in the healthcare system but also to increase the transparency and reasonableness of decisions.

für den AT Kontext gibt es noch einige offene Fragen zu klären

For the Austrian context, the first question that needs to be addressed is whether economic evaluations should generally play a more formal and explicit role in reimbursement decisions (Chapter 5.3). A positive answer to this question requires further decisions regarding the detailed methods for conducting HEE, whether or not to specify a threshold, which method to use to do so and in which way criteria beyond efficiency might be considered. Making the decisions as well as the methods transparent may increase trust among stakeholders and familiarity with the subject which will all be required for dealing with a genuinely sensitive topic. To support these decisions, we have listed the pros and cons of alternative approaches and (research) activities that would be required alongside.

6.5 Limitations

Limitationen:

One main limitation of our report is the method of identifying countries with potential thresholds. Five scientific publications were a starting point for identifying potential countries. In addition, the ISPOR guideline overview was consulted, focusing on countries from Europe and countries with similarities to the Austrian healthcare system. For this reason, the country selection does not represent a "complete survey" and may miss some countries from other continents.

Identifikation der Länder mit Schwellenwerten → keine Vollerhebung

Regarding the literature search, we opted for a structured manual search instead of a systematic search in scientific databases. We were specifically interested in how thresholds and modifiers are used in actual reimbursement decisions and not just in the academic discourse. The report does, therefore, not capture the entire scientific literature on the topic.

keine systematische Suche, da Fokus auf tatsächliche Anwendung von Schwellenwerten

The grouping of the modifying criteria is not mutually-exclusive as there may be some overlaps between criteria categories. Some information from certain countries was not specific enough to make a clear classification. For example, the criteria orphan drug designation or availability of therapeutic alternatives could be subsumed under the equity criterion. However, general equity related aspects like horizontal and vertical equity could not be classified under one of the other categories. Nevertheless, we tried to be as specific as possible and assigned countries with a specific modifier to one specific criterion group to avoid "double counting". However, in some cases a one-to-one correspondence was not possible.

Klassifizierung/ Gruppierung der Modifikatoren:

möglicherweise einige Überschneidungen

We did not adjust for PPP in the analysis of the ICER thresholds. Usually, economic output figures like the GDP are adjusted for price differentials. However, the rationale for this approach is that conventional PPP adjustment approaches may not be adequate [245], and countries' underlying consumer baskets (used to define PPP), including commodities and especially services, differ across countries. Furthermore, thresholds are not an output measure such as GDP but rather reflect the specific jurisdiction's valuation and the production- or resource-related affordability given the jurisdictions' prices for health care interventions. In addition, both factors are also considered by pharmaceutical companies and manufacturers of medical devices when setting the maximum achievable prices in their product portfolio and in price negotiations with each jurisdiction.

keine PPP-Adjustierung

→ Vergleichbarkeit potenziell eingeschränkt

Within the descriptive analysis, we only fitted simple linear regression models to get an idea of the relation between the threshold and GDP per capita and the threshold and HLE. However, the results must be interpreted with caution. Therefore, no in-depth inferential tests were conducted. A more variable-rich model would be necessary to get a fuller picture of the relation of these variables and valid estimates. Other covariates, such as country-specific preferences, values, or socioeconomic factors, may explain more of the threshold variation across jurisdictions. Therefore, a more in-depth scientific investigation is indicated.

vorsichtige Interpretation der Ergebnisse & Zusammenhänge der deskriptiven Analyse

→ weitere wissenschaftliche Analysen notwendig

7 Conclusion

Ziel des Berichts: Übersicht ges.ök. Konzepte & Grundlagen von HEE mit Fokus auf ICER-Schwellenwerte

This report aimed to introduce health economic thinking and ICER thresholds for a non-exclusive health economics audience. Furthermore, we wanted to give an overview of how these concepts are used to consider efficiency in reimbursement decisions and how they are applied internationally. Our goal was to provide decision makers and policy makers in Austria with an orientation for possible ways to implement such health economic methods more routinely and transparently.

unterschiedliche Ansätze zur Herleitung von Schwellenwerten existieren

Nicht-Effizienz-Aspekte fließen in einigen Ländern in Entscheidungen mit ein → Modifikatoren

The results demonstrate that economic evaluation and thresholds are based on different theoretical principles. Furthermore, various methods exist and have been applied in countries to conduct economic evaluations and define thresholds. We have also learned that many countries explicitly consider criteria beyond efficiency to reflect societal and political preferences on priorities in health care spending. Importantly, contrary to what the quantitative nature of most methods described might suggest, none of them are value-neutral pure technical or mathematical exercises. They rest on underlying ethical and equity values, significantly impacting how resources are allocated in a healthcare system.

Berücksichtigung von Effizienzaspekten ist ein ethischer Imperativ

Entscheidung über Berücksichtigung von ges.ök. Aspekten aber Aufgabe der Entscheidungsträger & Politik

A conclusion we draw from the report is that considering efficiency in reimbursement decisions is an ethical imperative for spending public resources. The question is, therefore, not if but how to integrate efficiency and potential modifiers more consistently and transparently in the reimbursement processes in Austria to also improve the reasonableness of decisions. As the variety of approaches countries follow demonstrates, there is no gold standard. Each approach has pros and cons regarding methodological and conceptual strengths and limitations, as well as the effort required for implementation. While, as researchers, we cannot prescribe an approach, the report can serve as a basis for selecting and comprehensibly justifying an approach for Austria. The final decision needs to be made at the policy level.

weitere Forschung zu ges.ök. Konzepten im Kontext der politischen Ökonomie notwendig

Finally, the results also showed a need for research and awareness raising that would be required alongside implementing such methods in Austria next to more general and international research on the concept and political economy of the threshold.

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Appendix

Table Countries with ICER Thresholds

Table A-1: Countries with ICER thresholds

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Australia	Mixed model[46]	50,000[47]	AUD	34,282.04	32,966.31	PBAC ICERs matched with NICE's ICERs of submitted technologies	56,144.85	57,924.23	70.61	QALY	No [218]	SubG	Implicit threshold matched to NICE's explicit ICER threshold (informal)	[1, 12, 101, 142, 144, 218, 257]
Austria	Bismarck model	No	EUR	Not applicable	Not applicable	Not applicable	62,545.04	44,362.96	69.79	Not applicable	No threshold [29]	PER	No threshold	[15, 29]
Belgium	Bismarck model	No	EUR	Not applicable	Not applicable	Efficiency frontier approach	60,277.93	41,988.29	69.79	Not applicable	No threshold [132]	PEG	No threshold; other factors more decision-relevant	[16, 132]
Brazil	Beveridge model	45,591.49-136,774.47 (2022 local currency unit)	BRL	17,216.45-51,649.34	8,380.94-25,142.83	1-3 x GDP per capita[48]	17,216.45	8,380.94	61.83	DALY and QALY	Yes [145]	PEG	Implicit threshold range (informal)	[16, 17, 145, 258]

[45] The classifications of the different healthcare systems are mainly taken from the European Observatory on Health Systems and Policies [19], Ferreira et al. [2018], and were reassured by further sources.

[46] Australia combines features of the Beveridge model, National Health Insurance Model, and the Bismarck model.

[47] Zhang and Garau [2020] reference to the threshold estimated by Wang et al. [2018]. Paris and Belloni [2013] report that technologies with an ICER greater than AUD 75,000/QALY (€ 49,449) were rarely recommended and technologies with an ICER greater than AUD 45,000/QALY (€ 29,670) only in rare circumstances [101]. A publication by Edney et al. [2018] empirically estimated an ICER threshold to publicly fund new health technologies of AUD 28,033 (€ 18,483) per QALY gained. The publication also mentions that summary documents from the PBAC have referred to the need to bring prices down so that ICERs are reduced to a value between AUD 45,000 (€ 29,670) and AUD 75,000 (€ 49,449) [144].

[48] *"Technologies with an ICER (monetary unit/DALY avoided) of less than one times the GDP per capita would be considered very cost-effective; up to three times the GDP per capita, still cost-effective; those with an ICER above three times the GDP per capita would be considered not cost-effective"* [145, p. 84]. Pichon-Riviere et al. [2023] estimated by relating health expenditures and life expectancy that the threshold should be 0.62-1.05 x GDP per QALY.

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Bulgaria	Mixed model (social health insurance contributions and taxes)	No[49]	BGN	Not applicable	Not applicable	Not applicable	30,884.54	9,073.4	62.39	Not applicable	Not available	Not applicable	No threshold	[166]
Canada	NHIM	Non-oncology: 50,000[50] Oncology: 100,000[51]	CAD	Non-oncology: 40,053.15 Oncology: 80,106.30	Non-oncology: 36,509.68 Oncology: 73,019.35	No specific method	54,028.98	42,965.79	69.78	QALY	No [147]	PEG	Implicit threshold (informal)	[1, 12, 101, 147, 148, 259, 260]
China	Mixed model[52] with a high proportion of OOP	77,630.09-232,890.27[53] (2022 local currency unit)	RMB	19,968.48-59,905.45	10,982.23-32,946.69	1-3 x GDP per capita	19,968.48	10,982.23	68.58	QALY	Yes [151]	PER	Implicit threshold (informal)	[154, 262, 263]

[49] A survey among Eastern European countries reports that Bulgaria has an official threshold of € 29,700. Whether this amount is explicitly or implicitly applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160].

[50] Two other publications estimated a threshold of CAD 80,000/QALY (€ 58,415) for the period 2003-2007 [143].

[51] Information on both threshold values are based from an interview in Zhang and Garau [2020]. They report that the thresholds are outdated. New guidelines by the Patented Medicines Price Review Board (PMPRB) should come into force. However, whether the PMPRB guidelines are into force by now is not clear from the official website [149]. Thokala et al. [2018] report on the basis of Griffiths and Vadlamudi [2016] that the threshold of CAD 50,000/QALY (€ 36,509.68) is not consistently applied. The new guidelines state that the ICER will be compared against the applicable Pharmacoeconomic Value Threshold based on based on four Therapeutic Criteria Levels: Level 1 (CAD 200,000/QALY [€ 146,039]): *"The patented medicine is the first medicine to be sold in Canada that effectively treats a particular illness or effectively addresses a particular indication"*. Level 2 (CAD 150,000/QALY [€ 109,529]): *"The patented medicine provides a considerable improvement in therapeutic effect, relative to other medicines sold in Canada, in a clinically impactful manner"*. Level 3 (CAD 150,000/QALY [€ 109,529]): *"The patented medicine provides moderate absolute improvement in therapeutic effect, relative to other medicines sold in Canada"*. Level 4 (CAD 100,000/QALY [€ 73,019]): *"The patented medicine provides slight or no improvement relative to other medicines sold in Canada"*. The criteria descriptions of each level are more extensive and are reported in the guideline [146]. For example, Level 2 and 3 medicines have the same threshold, but the final prices of medicines from these two different levels differ regarding the reduction cap applied to the maximum list prices used in price negotiations.

[52] The healthcare system in China is still evolving and has characteristics of the different systems. In 2016, China launched a new round of reform of the national healthcare system, the Healthy China 2030 Plan, which also states that HTA and pharmacoeconomic evaluations of pharmaceutical products will play a more central role in resource allocation [151-153]. Generally, the Chinese healthcare system is a universal health insurance system with a high share of out-of-pocket payments. The percentage of out-of-pocket payment in total health expenditure in China declined from 60% in 2001 to 28.8% in 2016 [261].

[53] A publication evaluated a WTP threshold of RMB 128,000/QALY (€ 18,108) for chronic diseases, RMB 149,500/QALY (€ 21,150) for rare diseases, and RMB 140,800/QALY (€ 19,919) for terminal diseases. These thresholds correspond to 1.76, 2.06 and 1.94 times the GDP per capita in China [154]. A publication by Ochalek et al. [2020] estimated a threshold range of RMB 27,923–52,247 (2017 RMB) (€ 3,950-7,391) per DALY averted corresponding to 47-88% of GDP per capita.

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Croatia	Mixed model (salary contributions and taxes)	No threshold	EUR	Not applicable	Not applicable	Not applicable	38,085.73	15,876.43	66.80	QALY	No threshold [264]	PER	No threshold	[264]
Czech Republic	NHIM	472,291.91-1,416,875.73[54] (2022 local currency unit)	CZK	46,344.79-139,034.38	19,225.43-57,676.29	1-3 x GDP per capita[55]	46,344.79	19,225.43	66.66	LYG and QALY	Yes [155]	SubG	Implicit threshold (informal)	[1, 155, 166, 265]
Denmark	Beveridge model[56]	No	DKK	Not applicable	Not applicable	Not applicable	67,663.13	57,328.28	70.06	QALY	No threshold [268]	PER	No threshold so far[57]	[267-270]
England and Wales	Beveridge model	20,000-30,000[58] (2022 local currency unit)	GBP/£	24,000-36,000	23,453.26-35,179.89	No specific method[59]	51,789.96 (UK)	44,976.30 (UK)	68.64 (UK)	QALY	Yes [158]	SubG	Explicit threshold range	[1, 12, 13, 158]

[54] The Czech submission guideline reports the use of a threshold of CZK 1.2 million/QALY (€ 48,848) and reports that CZK 1.0-1.2 million/QALY (€ 40,706.67- 48,848) is an acceptable threshold [155].

[55] Since 2013, when the SUKL's methodology SP-CAU-028 for cost-effectiveness assessment was published, the WHO-CHOICE threshold and methodology were adapted as a valid analysis framework. In borderline cases, (ICER between CZK 0.9-1.2 million/QALY [€ 36,636-48,848]), greater account will be taken of the uncertainties associated with the input data (sensitivity analysis) [155]. The guideline by the Czech Pharmacoeconomic Society (CFES) also mentions the WHO threshold approach to be adequate [156].

[56] The Danish Medicines Council makes decisions in cases concerning application for general reimbursement for medicinal products [266] and prepares recommendations and makes the decision on new medicines restricted to use at hospitals [267].

[57] The Danish Medicines Council (DMC) started a HTA processes in November 2020 moving to a QALY-based evaluation system. So far, Denmark did not publish an ICER threshold, but a study that analysed recent DMC recommendations estimated an ICER threshold to fall between DKK 458,134-969,518/QALY (€ 61,580-130,319) [269]. Further modifiers, such as disease severity, influencing recommendations and decisions were not considered in the analysis [270].

[58] The upper bound of the threshold, £ 30,000/QALY (€ 35,180), applies in the case of certainty of the ICER, inadequately evaluated HRQoL, and innovations [8, 17, 157, 158].

[59] NICE's ICER threshold range has little theoretical and empirical basis: *"The committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective or below which it would. Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies. NICE does not have complete information about the costs and QALYs from all competing healthcare programmes to define a precise maximum acceptable ICER. However, NICE considers that it is most appropriate to use a range as described in sections […]. Also, consideration of the cost effectiveness of a technology is necessary but is not the only basis for decision making. Consequently, NICE considers technologies in relation to this range of maximum acceptable ICERs, so that the influence of other factors on the decision to recommend a technology is greater when the ICER is closer to the top of the range."* National Institute for Health and Care Excellence (NICE) [2023, p. 173]

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Estonia	NHIM: Estonian Health Insurance Fund (hospital setting) and Ministry of Health (outpatient setting)[60]	20,083.95-60,251.84	EUR	41,663.26-124,989.77	20,083.95-60,251.84	1-3 x GDP per capita[61]	41,663.26	20,083.95	66.74	QALY	No [272]	PEG	Explicit threshold range	[2, 161]
Finland	Beveridge model	No threshold	EUR	Not applicable	Not applicable	Not applicable	55,481.54	44,322.41	69.93	QALY	No threshold [273]	SubG	No threshold	[273, 274]
France	Bismarck model	No threshold	EUR	Not applicable	Not applicable	Efficiency frontier approach	52,238.92	36,875.66	70.08	QALY	No threshold [131]	PEG	No threshold but efficiency frontier approach	[131]
Germany	Bismarck model	No threshold	EUR	Not applicable	Not applicable	Not applicable (used efficiency frontier approach in the past)	59,475.2	41,193.12	68.93	QALY	No threshold [10]	PEG	No threshold so far[62]	[10, 275]
Greece	Mixed model (transition phase from Bismarck to Beveridge model)[63])	19,273.34-57,820.02[64] (2022 local currency unit)	EUR	33,562.35-100,687.04	19,273.34-57,820.02	1-3 x GDP per capita	33,562.35	19,273.34	68.55	QALY	Not available	Not applicable	Implicit threshold (informal)	[162, 163]

[60] In 2023, Estonia presented its pharmaceutical policy 2030 in Estonian [271]. Hence, whether the division of competencies changed cannot be answered.

[61] A survey among Eastern European countries reports that Estonia has an official threshold of € 20,000/QALY. Whether this amount is explicitly or implicitly applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160]. Another publication from 2018 states that for a positive reimbursement decision, the ICER/QALY must be below € 40,000 [161].

[62] IQWiG's guidelines state that the application of a universal threshold value is currently not intended, as this is not the subject of IQWiG's assessment. The assessment of economic appropriateness is the responsibility of the decision maker [10]. A model-based study from 2023 estimated that a threshold value of nearly € 90,000/LYG for life-prolonging new, innovative health technologies (e.g., drugs) in Germany would not negatively impact the efficiency of the German health care system [275].

[63] The current HTA process in Greece only includes medicinal products. A Committee for the Negotiation of Medical Devices' Fees and Prices does exist, but is not involved in the assessment of new medical devices [162].

[64] A study estimated a potential ICER threshold for Greece by a contingent value approach. The mean WTP/QALY is € 26,280/QALY. Considering outliers by a 5% trimming approach, the WTP/QALY decreased to € 14,862 [163]. A survey among Eastern European countries reports that Greece has an unofficial threshold of € 30,000/QALY. Whether this amount is applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160].

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Hungary	NHIM	9,113,953.41-18,227,906.81 (2022 local currency unit)	HUF	57,996.89-115,993.77	23,292.07-46,584.14	1.5-3 x GDP per capita[65]	38,664.59	15,528.05	64.84	QALY	Yes [165]	PER	Implicit threshold classes (only re-commendation)	[16, 165, 166, 276]
Ireland	Beveridge model	45,000	EUR	46,333.33	45,000	No specific method[66]	116,466.01	92,451.03	70.00	QALY	Yes [167]	PEG	Explicit threshold[67] only for phar-maceutical interventions	[1, 8, 167, 168, 277, 278]
Israel	NHIM	No threshold	ILS	Not applicable	Not applicable	Not applicable	45,902.95	40,575.24	70.76	QALY	No threshold [279]	SubG	No threshold	[279]
Italy	Beveridge model	No threshold[68]	EUR	Not applicable	Not applicable	Not applicable	49,457.32	31,617.27	70.56	QLAY	No threshold [281]	PER	No threshold	[280, 281]
Japan	Bismarck model	5,000,000[69]	JPY	44,761.7	36,224.01	No specific method	42,915.99	34,392.51	73.40	QALY	No [282]	PEG	Implicit threshold[70] (informal)	[1, 169-171, 282, 283]

[65] The Hungarian guideline has the following rule for non-rare diseases: If the value of the health excess gain, i.e., 1 minus the ratio of the QALYs of the comparator and the QALYs of the technology under investigation, is between 0.00 and 0.25, the threshold is 1.5 x GDP per capita, between 0.25 and 0.60, the threshold is twice the GDP per capita, and between 0.60 and 1.00, the threshold is 3 x GDP per capita. An older publication states that in Hungary health technologies are declared as cost-effective under the threshold of 2 x GDP per capita/QALY, and proclaimed not cost-effective if the ICER is higher than 3 x GDP per capita/QALY [166]. Although, the threshold class approach considers health excess gains, which could be interpreted as a modifier for the threshold, this approach is listed here as it uses a modification of the WHO-CHOICE approach. Hungary applies orphan diseases as a particular modifier.

[66] Health Information and Quality Authority's (HIQA) threshold has little theoretical and empirical basis: *"Historically, the threshold has varied between € 20,000 and € 45,000 per QALY, although reimbursement below these levels was not guaranteed, and technologies above these thresholds have been adopted. For reporting purposes, it is pragmatic to report the probability of cost-effectiveness at thresholds of € 20,000 and € 45,000 per QALY. It is important to note that these thresholds have not been derived empirically. While consideration of the cost- effectiveness of a technology is necessary, it is not the sole basis for decision- making."* Health Information and Quality Authority (HIQA) [2020, p. 55]

[67] Reimbursement is guaranteed for new medicinal products with an ICER below the upper threshold of € 45,000 [168]. The probability of cost-effectiveness at thresholds of € 20,000 and € 45,000 per QALY is also reported for reporting purposes [167].

[68] One publication estimated a mean incremental cost per QALY gained of medicines based on company dossiers submitted to the Italian Medicines Agency of € 30,000/QALY [280].

[69] A study examined the WTP value for one additional QALY in a sample of 2,400 respondents. The WTP ranged from JPY 2,000,000 to 8,000,000/QALY (€ 14,490-57,958) depending on the severity of health states [171].

[70] The Central Social Insurance Medical Council (Chuikyo) reached a consensus to use JPY 5 million/QALY as the ICER threshold. If the ICER of a product is less than JPY 5,000,000/QALY (€ 36,224), its price is not adjusted. If the ICER is between JPY 5 million (€ 36,224) and 10 million/QALY (€ 72,448), the price adjustment rate increases stepwise. If the ICER is over JPY 10 million/QALY (€ 72,448), the price is adjusted at the maximum rate [170].

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Lativa	Mixed model (Beveridge/tax-financed with high proportion of OOP)	ICER of new intervention ≤ ICER of pharmaceuticals already reimbursed[71]	EUR	Not applicable	Not applicable	ICER of new intervention ≤ ICER of pharmaceuticals already reimbursed	36,069.09	16,163.89	63.76	LYG	No [272]	PEG	Implicit threshold (informal)	[2, 160, 172]
Lithuania	NIHM	No threshold[72]	EUR	Not applicable	Not applicable	Not applicable	44,674.16	17,608.32	64.23	LYG	No threshold [272]	PEG	No threshold	[2, 160]
Nether-lands	Bismarck model	20,000[73]	EUR	21,140.68	20,000	No specific method for the base -case threshold (€ 80,000/QALY is the maximum reference value per QALY gained; see Table A-2)	66,455.99	48,019.45	69.97	QALY	Yes [173, 174]	PEG	Implicit threshold (informal)	[1, 12, 109, 173-175, 210-212]
New Zealand	Beveridge model	No threshold	NZD	Not applicable	Not applicable	Not applicable	47,000.53	40,430.99	69.98	QALY	No threshold [284]	PEG	No threshold	[284]
Norway	Beveridge model	275,000[74] (2020 local currency unit)	NOK	25,871.40	27,220.72	No specific method for the baseline threshold	86,515.17	75,462.89	71.16	QALY	No [177][75]	PEG	Implicit thresholds	[1, 8, 176]

[71] A survey among Eastern European countries reports that Latvia has an official threshold of € 52,300/QALY. Whether this amount is explicitly or implicitly applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160].

[72] A survey among Eastern European countries reports that Lithuania has an official threshold of € 39,800/QALY. Whether this amount is explicitly or implicitly applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160].

[73] The baseline threshold is € 20,000 per QALY, and the maximum reference value is € 80,000 per QALY gained depending on other factors, such as severity of disease [109]. The authors van Baal et al. [2019] estimated a k-threshold of € 41,000 based on the marginal returns to medical care. This threshold almost corresponds to the suggested implicit baseline threshold. Another publication by Stadhouders et al. [2019] estimated a threshold of € 73,600 per QALY (95% CI: € 53,000 to € 94,000). This estimate is greater than the baseline threshold and reflects almost to the maximum reference threshold of € 80,000 for reimbursement decisions considering further factors [175].

[74] This threshold value is based on information from an interview in Zhang and Garau [2020].

[75] The Norwegian guideline does not mention any specific threshold but reports the method to account for disease severity. Disease severity has also an impact on the application of the informal thresholds (see Table A-2) [177].

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Norway *(continuation)*						("opportunity cost approach" based on the condition- or disease-associated health loss; see Table A-2)							(thresholds have never examined and approved by the parliament, informal)	
Poland	Beveridge model:	229,427.73 (2022 local currency unit)[76]	PLN	124,881.31	48,959.20	3 x GDP per capita	41,627.10	16,319.73	65.52	QALY or LYG	No [179]	SubG	Explicit (legislated)	[1, 124, 166, 285]
Portugal	NHIM	30,000[77]	EUR	41,287.13	30,000	No specific method	39,178.37	21,019.64	69.52	QALY	No [183]	PEG	Implicit threshold (informal)	[16, 181-183]
Scotland	Beveridge model	20,000-30,000 (2022)	GBP/£	24,000-36,000	23,453.26-35,179.89	No specific method (see England & Wales)	51,789.96 (UK)	44,976.30 (UK)	68.64 (UK)	QALY	Yes [184]	SubG	Implicit threshold (informal)	[1, 224, 286]
Singapore	Mixed model (nationalised life insurance scheme with private premiums)	No threshold	SGD	Not applicable	Not applicable	Not applicable	125,845.48	64,551.45	73.65	QALY	No threshold [287]	PEG	No threshold	[287]

[76] Zhang and Garau [2020] report a threshold of PLN 146,937/QALY (2016 local currency unit) (€ 31,356) and Orlewska et al. [2022] report a threshold of PLN 147,024/QALY (€ 31,375). The difference may be due to the difference in the used GDP approach and the different exchange rate.

[77] A study on the clinical impact and cost-effectiveness of routine HIV Screening in Portugal states that *"Anecdotal evidence suggests that the Portugues National Authority of Medicines (Infarmed) adopts an informal threshold of 30,000/QALY in determining whether a given pharmaceutical intervention is cost-effective. This threshold is inspired by the United Kingdom National Institute for Health and Clinical Excellence (NIHCE) guidelines"* [180]. A publication by Laires et al. [2015] investigating the cost-effectiveness of statin monotherapy also state that *"Considering the Portuguese cost-effectiveness willingness-to-pay threshold of € 30,000/QALY, adding ezetimibe vs switching to rosuvastatin would be a cost-effective use of resources in Portugal"*. A CUA of genetic polymorphism universal screening in colorectal cancer prevention set the threshold at € 44,870, which complies with the US ICER threshold of USD 50,000 (€ 47,483) [182]. The Portugues guideline states that the *presentation of health economic results* should consider opportunity costs using threshold ranges between € 10,000/QALY and € 100,000/QALY [183].

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
South Korea	NHIM:	43,466,198[78] (2022)	KRW	47,437.28	32,006[78]	1 x GDP per capita	47,437.28	32,005.86	72.45	QALY	Unclear due to language barriers [187]	Not applicable	Implicit threshold (informal)	[1, 187, 288]
Slovak Republic	Mixed model (Bismarck, Beveridge, NHIM)	53,859.42	EUR	110,030.83	53,859.42	3 x GDP per capita[79]	36,676.94	17,953.14	77.07	QALY	Yes [188]	Not applicable	Explicit threshold	[2, 189]
Slovenia	Bismarck model	25,000 & 30,000[80]	EUR	34,866.22-41,839.47	25,000 & 30,000	No specific method	45,180.36	24,082.27	69.36	QALY	No guideline, but regulation [194]	Not applicable	Explicit threshold	[190-193]
Spain	Beveridge model	21,000[81]	EUR	27,365.63	21,000	Empirical ICER threshold	43,498.31	26,317.61	71.11	QALY	Yes [289]	PER	Implicit threshold (informal)	[196, 289]

[78] Zhang and Garau [2020] report a value of KRW 25,000,000 (€ 18,408.48) which was reported in Bae et al. [2018] and should reflect the 1 x GDP per capita threshold. However, the converted 1 x GDP per capita threshold using the World Bank data is KRW 43,466,198 (€ 32,006). For the analysis, we used the value based on our GDP per capita calculation. A publication from 2022 listed studies from Korea that estimated the social value of a QALY by a WTP approach at the national level using EQ-5D scenarios. The WTP ranged from KRW 15 million/QALY (€ 11,045) to KRW 40.28 million/QALY (€ 29,660) depending on the severity of the diseases (mild symptoms, moderated symptoms, sever symptoms, severe terminal disease, immediate death) [186]. Another publication from 2010 elicited a WTP/QALY of KRW 68,000,000 (€ 50,071) [171].

[79] The Ministry of Health of the Slovak Republic approved the Act. No 363/2011 governing access to medicines and innovation for Slovak patients [188]. Within this act, the baseline threshold value was increased to 3 x GDP per capita. For most drugs, the threshold is set at 3 x GDP per capita of two years ago per QALY, as long as the drug adds at least 0.33 QALYs. In the case of a lower contribution, 2 x GDP per capita per QALY is applied. The threshold for orphan drugs was set to 10 x GDP per capita [189]. A survey among Eastern European countries reports that the Slovak Republic has an official threshold of € 40,000. Whether this amount is explicitly applied cannot be validly inferred, because only the abstract of this publication with limited information on the methods is available [160]. Garcia-Mochon et al. [2019] reported a threshold of 24 x average monthly salary and 35 x average monthly salary based on interviews conducted before 2019.

[80] According to a document by the Health Insurance Institute of Slovenia (Zavod za zdravstveno zavarovanje Slovenije, ZZZS) from 2013, the threshold for medicines reimbursed by ZZZS is € 25,000/QALY [190-192]. The Health Council, the supreme counselling body to the Ministry of Health of the Republic Slovenia, sets a threshold of € 30,000/QALY [193].

[81] The Spanish pharmacoeconomic recommendation for hospital medicines published in November 2016 states that the current threshold is € 21,000/QALY, which replaced the threshold of € 30,000/QALY commonly used in the past. A health economic study on palivizumab for respiratory syncytial virus infection prophylaxis in preterm infants submitted in February 2017 also reports that a threshold of € 30,000/QALY is commonly accepted in Spain [196]. According to the Spanish pharmacoeconomic guideline report commissioned by the Spanish Ministry of Health and Ministry of the Canaries, the basis for the identified threshold is a report by Vallejo-Torres [2015]. The authors estimated a threshold range of € 21,000 and 24,000 per QALY and recommended that a threshold range of € 20,000 to 25,000 per QALY should be used in the Spanish national healthcare system.
In a publication from 2016, Vallejo-Torres et al. [2016] re-estimated the threshold range, resulting in a range of €22,000 and 25,000 per QALY. In Spain, the Ministry of Health also provides a guideline for economic evaluation of pharmaceuticals but does not report on a threshold [197].

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
Sweden	Beveridge model	500,000[82]	SEK	47,123.97	47,038.46	No specific method ("Rule of thumb")[83]	61,390.47	53,099.45	71.12	QALY	Yes [198-200]	PEG	Implicit threshold (informal)	[1, 8, 12, 198-200, 202, 290]
Switzerland	Bismarck model	No threshold	CHF	Not applicable	Not applicable	Not applicable	78,868.85	85,554.18	71.15	Not applicable	No threshold [291]	PEG	No threshold (application of HEE and thresholds is currently in an elaboration phase)	[291-293]
Taiwan	NHIM	No threshold[84]	TWD	Not applicable	Not applicable	Not applicable	65,778	30,979.5[85]	69.90	QALY	No threshold [296]	PEG	No threshold	[294-297]
Thailand	Mixed model[86]	160,000 (2020)	THB	11,017.17	4,341.22	No specific method	19,714.97	5,962.13	65.76	QALY	Not available[87]	Not applicable	Explicit threshold	[1, 139-141, 222, 223]

[82] This threshold value is based on information from an interview in Zhang and Garau [2020]. The threshold is also a "rule of thumb" in the Swedish policy debate [202]. The HTA guideline by the SBU states that TLV's subsidy (reimbursement) decision can also be used to estimate the threshold value for what can be considered cost-effective in Sweden. The National Board of Health and Welfare categorise an ICER as low (SEK <100,000 [€ 9,408]), moderate (SEK 100,000-499,999 [€ 9,408-47,038]), high (SEK 500,000-1,000,000 [€ 47,038-94,077]) or very high (>SEK 1,000,000 [€ 94,077]) [200]. Although the SBU provides a HTA guideline, the only governmental agency that has an official and mandatory guideline for how to perform an economic evaluation is the TLV [199, 201].

[83] Another publication estimated a threshold range of SEK 700,000-1,220,000/QALY (€ 65,854-114,774) using a regression analysis (RA) [202]. RA is statistical tool to estimate the relationship between a dependent variable and various independent variables. In this specific case the outcome variable was whether the intervention was reimbursed or not (binary). The explanatory and relevant variable was cost per QALY and severity of the disease was a control variable.

[84] Zhang and Garau [2020] report a threshold of TWD 1,199,237/QALY (USD 38,598 [€ 36,655]), which corresponds to 1 x GDP per capita (2016 LCU) of Taiwan. However, whether this threshold is informally accepted in Taiwan is not clear as the cited publication, the guideline and also other publications do not indicate the acceptance of this threshold [294-297].

[85] Data by the International Monetary Fund (IMF): Taiwan Province of China GDP per capita in current prices (2022).

[86] Thailand has a national health insurance with universal coverage. The national health insurance has three major schemes, the Civil Servant Medical Benefit Scheme (CSMBS), the Social Security Scheme (SSS), and the Universal Coverage (UC) scheme [298].

[87] According to Zhang and Garau [2020] and Isaranuwatchai et al. [2022], the threshold is mentioned in the Health Intervention and Technology Assessment Program's (HITAP) guideline. However, the guideline was not publicly available to check the validity.

Country	Type of healthcare system[45]	Threshold (local currency)	Currency	Threshold EUR PPP (2022)	Threshold EUR (2022)	Underlying method	constant GDP (2021) per capita PPP in EUR (2022)	constant GDP (2015) per capita in EUR (2022)	Healthy life expectancy (HLE) at birth (2021)	Outcome measure	Threshold in guideline (Yes/No)	Guideline type	Notes	Sources
United States of America	Mixed model[88]	50,000-150,000[89] (2022)	USD	41,700-125,100	47,483.38-142,450.14	No specific method	68,557.21	60,534.73	63.91	QALY	Yes [206, 300]/ No [301]	PEG (US-ICER)/PER (AMCP)	Implicit threshold range (informal)	[1, 12, 101, 204, 206, 221, 300]

Abbreviations: AMCP … Academy of Managed Care Pharmacy, AUD … Australian Dollar, BGN … Bulgarian Lew, BRL … Brazilian Real, CAD … Canadian Dollar, CHF … Swiss Franc, DALY … Disability-Adjusted Life Year, DKK … Danish Krona, EUR … Euro, GBP/£ … British Pound, GDP … Gross Domestic Product, HEE … Health Economic Evaluation, HLE … Health Life Years, HUF … Hungarian Forint, ICER … Incremental Cost-Effectiveness Ratio, ILS … Israel Schekel, JPY … Japanese Yen, KRW … South Korean Won, LY … Life Years, LYG … Life-Year Gained, NHIM … National Health Insurance Model, NICE … National Institute for Health and Care Excellence, NOK … Norwegian Krona, NPRC … National Pricing and Reimbursement Council, NZD … New Zealand Dollar, OOP … Out of pocket payment, PBAC … Australian Pharmaceutical Benefits Advisory Committee, PBAC … Pharmaceutical Benefits Advisory Committee, PEG … Pharmacoeconomic Guideline, PER … Pharmacoeconomic Recommendation, PLN … Polish Zloty, PPP … Purchasing Power Parity, QALY … Quality-Adjusted Life Year, RMB … Renminbi, SEK … Swedish Krona, SGD … Singapore Dollar, SubG … Submission Guideline, THB … Thai Baht, TWD … Taiwanese Dollar, USD … United States Dollar, US-ICER … Institute for Clinical and Economic Review

Social security or healthcare systems can be classified into four basic models: Beveridge model (Universal healthcare model), Bismarck model (Social security model), National health insurance model (NHIM), Out-of-pocket model. Some countries cannot be assigned to one of the four basic models and have characteristics of a combination of the four models (mixed models). ISPOR defines three types of guidelines: Pharmacoeconomic recommendations (PER), pharmacoeconomic guidelines (PER), and Submission Guidelines (SubG). A detailed description of the different healthcare systems and the taxonomy of guidelines can be found in the section 2.4 Country Selection, Extracted Information, Country Overview.

[88] The US healthcare system has many separate systems for separate classes of people. Generally, it is a private insurance system but has mixed features: in 2023, 8.4% US Americans did not have a health insurance and would have pay for healthcare out-of-pocket [299], Medicare is a form of NIH, some employer-based healthcare plans reflect the Bismarck model, and the Veterans Health Administration in the U.S is a Beveridge-type model [20]. In the USA, there are several organisations that conduct HEE. However, there is no formal HTA process like in the UK or Germany and no "official" HTA institution that informs public decision makers on reimbursement decisions. Two of these organisations that provide health economic guidance are the Institute for Clinical and Economic Review, a nonprofit organization, and the Academy of Managed Care Pharmacy (AMCP), a professional organization representing the interest of pharmacists.

[89] The decision-relevant threshold range for a majority of new drugs are USD 50,000-150,000 (€ 47,483-142,450) according to some publications [204, 205]. This threshold range is also recommended by the recommended by the Institute for Clinical and Economic Review [206]. Furthermore, the economic modelling team at the Institute for Clinical and Economic Review conducted a long-term cost-effectiveness threshold analysis. They estimated that the intervention costs or prices lie within the commonly cited threshold range of USD 50,000 to USD 200,000 (€ 47,483-189,934) per QALY or equal value of life years gained (evLYG). The evLYG analysis accounts for improvements in patients' quality of life while counting any gains in length of life equally regardless of the quality of life [206, p. 40].

Table Countries with Modifiers

Table A-2: Countries with modifiers

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Australia	-	-	AUD	-	-	■ Severity of disease (Rule of rescue/ Unmet needs and presence of effective therapeutic alternatives) ■ Equity ■ Budget impact ■ Uncertainty of the ICER (cost and benefits)/Overall confidence ■ Public health relevance (development of resistance)	Modifiers are also mentioned in the guideline	[1, 143, 218]
Austria	Not available	Not applicable	EUR	-	-	Not available	-	
Belgium	Not available	Not applicable	EUR	-	-	Not available	Decision making in Belgium remains mainly an interactive deliberation process. Clinical effectiveness is the most important scientific criterion, but cost-effectiveness is sometimes considered in the Drug Reimbursement Committee (DRC) but rarely in the Technical Council for Implants (TCI), and budget impact is considered more important by both committees than the ICER.	[12]
Brazil	Not available	Not applicable	BRL	-	-	Not available	-	-
Bulgaria	Not available	Not applicable	BGN	-	-	Not available	-	-
Canada	■ Oncology	140,000	CAD	70,635.78	102,227.09	■ Horizontal and vertical Equity[90]	-	[1, 147]
China	Not available	Not applicable[91]	RMB	-	-	Not available	-	-
Croatia	Not available	Not applicable	EUR	-	-	Not available	-	-
Czech Republic	-[92]	-	CZK	-	-	■ Severity of disease ■ Highly innovative drugs (HID) for severe diseases with markedly higher efficacy, greater safety, or	The Czech Republic uses a two-tier reimbursement system: ■ permanent reimbursement ■ a 2- to 3-year TR period	[1, 219, 220]

[90] The Canadian guideline states that equity refers to notions of fairness and can be considered in terms of health and health care . Horizontal equity = equal people should be treated equally, Vertical equity = different people should be treated differently).

[91] A publication evaluated a WTP threshold of RMB 128,000 (€ 18,108) for chronic diseases, RMB 149,500 (€ 21,150) for rare diseases, and RMB 140,800 (€ 19,919) for terminal diseases. These thresholds correspond to 1.76, 2.06 and 1.94 times the GDP per capita in China [154].

[92] The Czech Republic does not have a modified threshold. However, a study estimated the mean ICER of drugs that entered temporary reimbursement status to be € 97,868 [219].

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Czech Republic *(cont.)*						no existing alternative treatment can apply for temporary reimbursement (TR)[93]		
Denmark	Not available	Not applicable	DKK	-	-	Not available[94]	-	-
England and Wales	■ Size of benefit for highly specialised technologies[95] (orphan diseases) ■ Severity of disease including end-of-life treatments/unmet need (by QALY weighting)[96]	■ 100,000-300,000 ■ 50,000 (end-of-life)	GBP/£	■ 120,000-360,000 ■ 60,000 (end-of-life)	■ 94,966.76-284,900.28 ■ 47,483.38 (end-of-life)	■ Budget impact[97]	To be transparent in decision making, when applying decision-making modifiers, net health benefits should be routinely presented to show the effect on opportunity costs	[1, 158, 215-217]
Finland	Not available	Not applicable	EUR	-	-	Not available	-	-
France	Not available	Not applicable	EUR	-	-	Not available	-	-
Germany	Not available	Not applicable	EUR	-	-	Not available	-	-

[93] The CFES proposes that in rare or highly rare disease areas (orphan diseases), in cases of unmet need, or in situations where the relationship between surrogate clinical outcomes and hard outcomes is not well studied or not detectable, the evaluation of other criteria should be used. It is not clear to what extent these criteria are considered in SUKL's assessment and decision-making process [156]. Furthermore, CFES states that social consequences of the disease and impact on family and carers should be accounted for by adapting a societal perspective in the HEE as it is the case in Sweden or Norway. Accounting for these additional criteria could reflect the social consequences of certain type of diseases (paediatric patients, patients with a disease causing significant disability). The consideration of social consequences affects the benefits and costs in the HEE and the ICER respectively, and not directly the ICER threshold.

[94] In Denmark, the relevant decision-making parties agreed on seven overall principles for prioritisation in the area of hospital medicines: Professionalism in the assessment process, independence of the assessment, geographical similarity and uniform application of medicines across the country, transparent assessment, fast adoption and rapid utilisation of new, effective medicines, rational use of budget funds ("more health for your money", equal access to care and high-quality treatment for patients with rare diseases to avoid disability [302].

[95] Highly specialised technologies can be understood as interventions for very rare conditions in the sense of orphan diseases. The basic threshold for highly specialised technologies is £ 100,000 (€ 94,967). For incremental QALYs gained over the lifetime less than or equal to 10 the weight is 1, between 11 to 29 additional QALYs the weight is 1 and 3 (using equal increments) and for QALY gains greater than or equal to 30 the weight is 3. Above a most plausible ICER of £ 20,000/QALY (€ 23,453), or £ 100,000/QALY (€ 94,967) for highly specialised technologies, decision makers will consider the degree of certainty and uncertainty around the ICER and aspects that relate to uncaptured benefits and non-health factors [158].

[96] Not applicable for diagnostics. For end-of-life therapies, the NICE introduced an additional guidance for end-of-life technologies [215]. The guidance allows the Appraisal Committee to give additional weight to quality-adjusted life-years (QALYs) benefits achieved at the end-of-life [215, 216]. The QALY weighting does only indirectly alter the ICER threshold but affects the ICER.

[97] In the case of England and Wales, the NICE and NHS have proposed doubling the Budget Impact Test (BIT) threshold to £ 40 million (€ 37,986,800), up from its current level of £ 20 million (€ 18,993,400) initially introduced in 2017. This change was outlined in a consultation document released on July 31, 2024. When a technology exceeds the BIT threshold, the NHS has the option to initiate commercial negotiations with the manufacturing company. These negotiations aim to address the financial challenges of implementing the technology, following the guidelines established in NHS's Commercial Framework for New Medicines [225]. The clinical evaluation and CEA of a technology by NICE remains independent from both the budget impact assessment and the BIT implementation [225, 226].

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Greece	Not available	Not applicable	EUR	-	-	Not available	-	-
Hungary	■ Rare diseases: Orphan treatments	3-10 x GDP per capita[98] (18,227,906.81-60,759,689.37)	HUF	115,993.77-386,645.9	46,584.12-155,280.4	-	The guideline recommends that in addition to the results of the health economic analysis, it is recommended that other aspects and domains are considered when assessing health technologies according to the EUnetHTA Core Model.	[16, 165, 166]
Ireland	■ Rare diseases: Ultra-rare diseases[99]	100,000	EUR	102,963.28	100,000	-	Cost-effectiveness is not the sole basis for decision-making in Ireland. Other factors such as equity issues, affordability, resource constraint, the strength of the evidence, and the uncertainty surrounding the results (such as validity of the data, range and plausibility of the ICERs, likelihood of error) have been considered on a decision to reimburse a technology.	[1, 167]
Israel	Not available	Not applicable	ILS	-	-	Not available	-	-
Italy	Not available	Not applicable		-	-	Not available	-	-
Japan	■ Rare diseases (patient need, burden of disease, severity of disease) ■ Paediatric labelling as part of indications ■ Products for cancer therapy	7,500,000	JPY	67,142.55	54,336.01	-	innovative products with a significant financial impact are regarded as the primary cases of cost-effectiveness evaluations	[1, 170]
Lativa	Not available	Not applicable	EUR	-	-	Not available [100]	All the pharmaceuticals included in the positive list are classified into one of three reimbursement categories (100%, 75%, and 50%). E.g. medicines for rheumatoid arthritis are fully reimbursed and three quarters of the cost of pharmaceuticals for inflammatory bowel diseases are reimbursed. In addition, the positive list consists of three sub-lists: reference price lists with groups of A) inter-changeable pharmaceutical products, B) noninter-changeable products, and C) high-cost pharmaceutical products with annual treatment costs exceeding € 4,300	[172, 303]

[98] Hungary applies a specific calculation scheme for orphan drugs. In the calculation the absolute value of the incremental discounted QALY between the technology under investigation and the comparator is relevant. For incremental discounted QALYs above 0.5 and below 20, the threshold varies proportionally between 3 and 10 x GDP per capita. For incremental discounted QALYs of 20 or more, the threshold is 10 x GDP per capita [165].

[99] The modifier and the associated threshold value are based on information from an interview in Zhang and Garau [2020].

[100] Silins and Szkultecka-Debek [2017] report that the NHS's reimbursement decision depends on several criteria: burden of disease, the therapeutic value of a pharmaceutical, correspondence to treatment schemes, cost-effectiveness of the product, and impact on the health care budget. However, another publication states that Latvia does not have any special laws or policies regarding orphan drugs different from the ones for non-orphan drugs and there is also not another (higher) ICER threshold for orphan drugs [303].

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Lativa *(cont.)*							(treatment with a particular pharmaceutical from list C has to be requested by a council of specialists)	
Lithuania	Not available	Not applicable	EUR	-	-	Not available	In Lithuania there is a formal HTA process implemented which does not include economic assessment. But there is a special law/policy regarding the reimbursement of orphan drugs and a special ultra-rare diseases reimbursement committee.	[303]
Nether-lands	■ Severity of disease (disease burden/ proportional shortfall)	20,001-80,000[101]	EUR	21,141.81-84,563.02	20,001-80,000	-	Proportional shortfall (PS)[102] was introduced to quantify necessity of care, allowing a direct equity-efficiency trade-off, but PS does not necessarily reflect societal preferences (Threshold values should be updated every five to ten years).	[1, 209-212]
New Zealand	Not available	Not applicable	NZD	-	-	Not available	-	[284]
Norway	■ Severity of disease (health loss by absolute shortfall[103])	275,000-1,000,000	NOK	25,871.40-94,077.8	27,220.72-98,984.43	-	Three criteria are crucial for systematic priority setting in the Norwegian healthcare system: health-benefit criterion, resource criterion and the health-loss criterion, but only the health-loss criterion should have an impact on the threshold.	[1, 8, 176, 209, 214]
Poland	Not available	Not applicable	PLN	-	-	Not available	-	[1, 124, 166, 285]
Portugal	Not available	Not applicable	EUR	-	-	Not available	-	[183]

101 Another publication reports and applies a threshold of € 50,000 in the context of sacubitril/valsartan use for heart failure patients [213].

102 The Netherlands have three threshold classes dependent on disease severity. Instead of health excess gains like Hungary, the disease burden (WHO's Global Burden of Disease) serves as a determinant for the class distinction of the threshold: A disease burden of 0.1 to 0.4 means a threshold of € 20,000/QALY, a disease burden of 0.41 to 0.7 means a threshold of € 50,000/QALY, and a disease burden of 0.71 to 1,0 means a threshold of € 80,000/QALY [174, 207]. The disease burden is calculated by the proportional shortfall approach. The PS approach is a method to consider the fraction of QALYs that people lose relative to their remaining life expectancy, and not on the absolute QALYs gain or loss [208].

103 Three criteria are crucial for systematic priority setting in the Norwegian healthcare system: the health-benefit criterion, resource criterion, and health-loss criterion. Only the health-loss criterion should have an impact on the threshold. Health-loss criterion: "*The priority of an intervention increases with the expected lifetime health loss of the beneficiary in the absence of such an intervention*" [176, p. 247]. Health-losses and the three threshold classes are calculated by the absolute shortfall (AS) approach according to the Norwegian guideline [177]. Absolute shortfall is defined as the absolute reduction in future healthy life years for people with the disease, when compared with what people at the same age but without the disease can expect. The Magnussen Working Group recommended that the lower bound of the threshold should be NOK 275,000, and that the upper bound of the threshold for the highest priority diseases/conditions should be three times higher, i.e. NOK 825,000. The group proposed six severity classes and report that some aspects of severity may not be captured by the AS approach [214]. (Severity classes based on AS and thresholds: 0 to 0.39, 4 to 7.9, 8 to 11.9, 12 to 15.9, 16 to 19.9, and >20 QALY; NOK 275,000/QALY (€ 25,871), NOK 385,000/QALY (€ 36,219), NOK 495,000/QALY (€ 46,568), NOK 605,000/QALY (€ 56,916), NOK 715,000/QALY (€ 67,265), and NOK 825,000/QALY (€ 77,613) [209]. Another publication reports that a commonly cited threshold in Norway is NOK 500,000/QALY (€ 47,038) [304].

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Scotland	-	-	EUR	-	-	■ Rare diseases: Orphan medicines ■ Evidence of a substantial improvement in life expectancy/quality of life/extra benefit for a subgroup ■ Absence of other therapeutic options of proven benefit ■ Possible bridging to another therapy ■ Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice	Scotland does not have a formal explicit threshold. Neither for general reimbursement decisions nor for orphan medicines. The threshold is only part of a wider judgment of the value of a new medicine. The modifiers are only applied for a relatively high cost per QALY when the committee is satisfied that the clinical and economic case for the medicine is robust.	[1, 184, 224, 305]
Singapore	Not available	Not applicable	SGD	-	-	Not available	-	-
South Korea	-	-	-	-	-	■ Severity of disease (cancer, rare diseases, diseases in terminal stage) ■ Availability of substitutes	Five factors were suggested as the most influential criteria in drug reimbursement decision-making: clinical improvement, cost-effectiveness, the severity and rarity of disease, and the availability of substitutes.	[1, 185]
Slovak Republic	■ Rare diseases: Orphan drugs including ATMPS	3.5-10 x GDP per capita:	EUR	366,769.4	62,836-179,531.41 (3.5 x 17 953.14; 10 x 17,953.14)	-	If a medicine loses orphan status, the Marketing Authorization Holder (MAH) will be obliged to submit a pharmacoeconomic analysis of the drug (FER) to the Ministry of Health within 120 days. If the drug is not cost-effective according to the basic threshold value anymore, it is removed from the list of medicinal products.	[188, 189]
Slovenia	Not available	Not applicable	EUR	-	-	Not available	-	-
Spain	Not available	Not applicable	EUR	-	-	Not available	-	-
Sweden	■ Rare diseases ■ Severity of disease	2,000,000[104]	SEK	188,496.08	188,153.83	-	In Sweden, the Swedish Dental and Pharmaceutical Benefits Agency (TLV) consider, according to law, disease severity and cost effectiveness for reimbursement decisions [6, 18].	[1, 202, 290]
Switzerland	Not available	Not applicable	CHF	-	-	Not available	In Switzerland, efficacy, appropriateness, and cost-effectiveness *("Wirtschaftlichkeit")* are cumulative requirements to be met by the intervention to be covered by health insurances. These basic requirements are regulated by law.	[291]
Taiwan	Not available	Not applicable	TWD	-	-	Not available	-	-

[104] Swedish law states that only disease severity and cost-effectiveness should be considered for reimbursement decisions [202]. The value of SEK 2,000,000 (€ 188,154) is based on information from an interview in Zhang and Garau [2020] and seem to apply for reimbursement decisions in the context on rare diseases. Whether this threshold also applies to severity of disease is not clear. Another publication reported on an ICER threshold of SEK 1,220,000 (€ 114,774) [290].

Country	Quantitative modifiers	Threshold (local currency)	Currency	Threshold PPP EUR (2022)	Threshold EUR (2022)	Qualitative modifiers	Other characteristics and notes	Sources
Thailand	-	-	THB	-	-	■ Equity[105]	-	[1, 139-141, 222, 223]
United States of America	■ High-Impact single and short-term therapies (SSTs)[106]	150,000 (2022)	USD	125,100	142,450.14		-	[1, 204, 206, 221, 300]
	■ Rare diseases: Ultra-Rare Conditions	500,000 (2022)		417,000	474,833.81			

Abbreviations: AMCP … Academy of Managed Care Pharmacy, AUD … Australian Dollar, BGN … Bulgarian Lew, BRL … Brazilian Real, CAD … Canadian Dollar, CHF … Swiss Franc, DALY … Disability-Adjusted Life Year, DKK … Danish Krona, EUR … Euro, GBP/£ … British Pound, GDP … Gross Domestic Product, HEE … Health Economic Evaluation, HLE … Health Life Years, HUF … Hungarian Forint, ICER … Incremental Cost-Effectiveness Ratio, ILS … Israel Schekel, JPY … Japanese Yen, KRW … South Korean Won, LY … Life Years, LYG … Life-Year Gained, NHIM … National Health Insurance Model, NICE … National Institute for Health and Care Excellence, NOK … Norwegian Krona, NPRC … National Pricing and Reimbursement Council, NZD … New Zealand Dollar, OOP … Out of pocket payment, PBAC … Australian Pharmaceutical Benefits Advisory Committee, PBAC … Pharmaceutical Benefits Advisory Committee, PEG … Pharmacoeconomic Guideline, PER … Pharmacoeconomic Recommendation, PLN … Polish Zloty, PPP … Purchasing Power Parity, QALY … Quality-Adjusted Life Year, RMB … Renminbi, SEK … Swedish Krona, SGD … Singapore Dollar, SubG … Submission Guideline, THB … Thai Baht, TWD … Taiwanese Dollar, USD … United States Dollar, US-ICER … Institute for Clinical and Economic Review

[105] Three scientific publications in the context of imiglucerase for Gaucher disease in Thailand report that it was included in the benefit package on account of equity considerations even though the agent did not provide good value-for-money [139, 222, 223]. The authors mention that imiglucerase was included, because it treats a very rare disease and the associated HEE estimated that there would be no more than five people who require treatment per year [139, 223]. Furthermore, if imiglucerase were not included, bone marrow transplantation, which is part of the benefits package, *"would mainly be available for the rich who are able to pay for imiglucerase before undertaking bone marrow transplantation"* [139].

[106] *"SSTs are defined as therapies that are delivered through a single intervention or a short-term course (less than one year) of treatment that offer a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes. SSTs include potential cures that can eradicate a disease or condition and high-impact therapies that can produce sustained major health gains or halt the progression of significant illnesses."* [206, p. 12].

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